

Endocrinology

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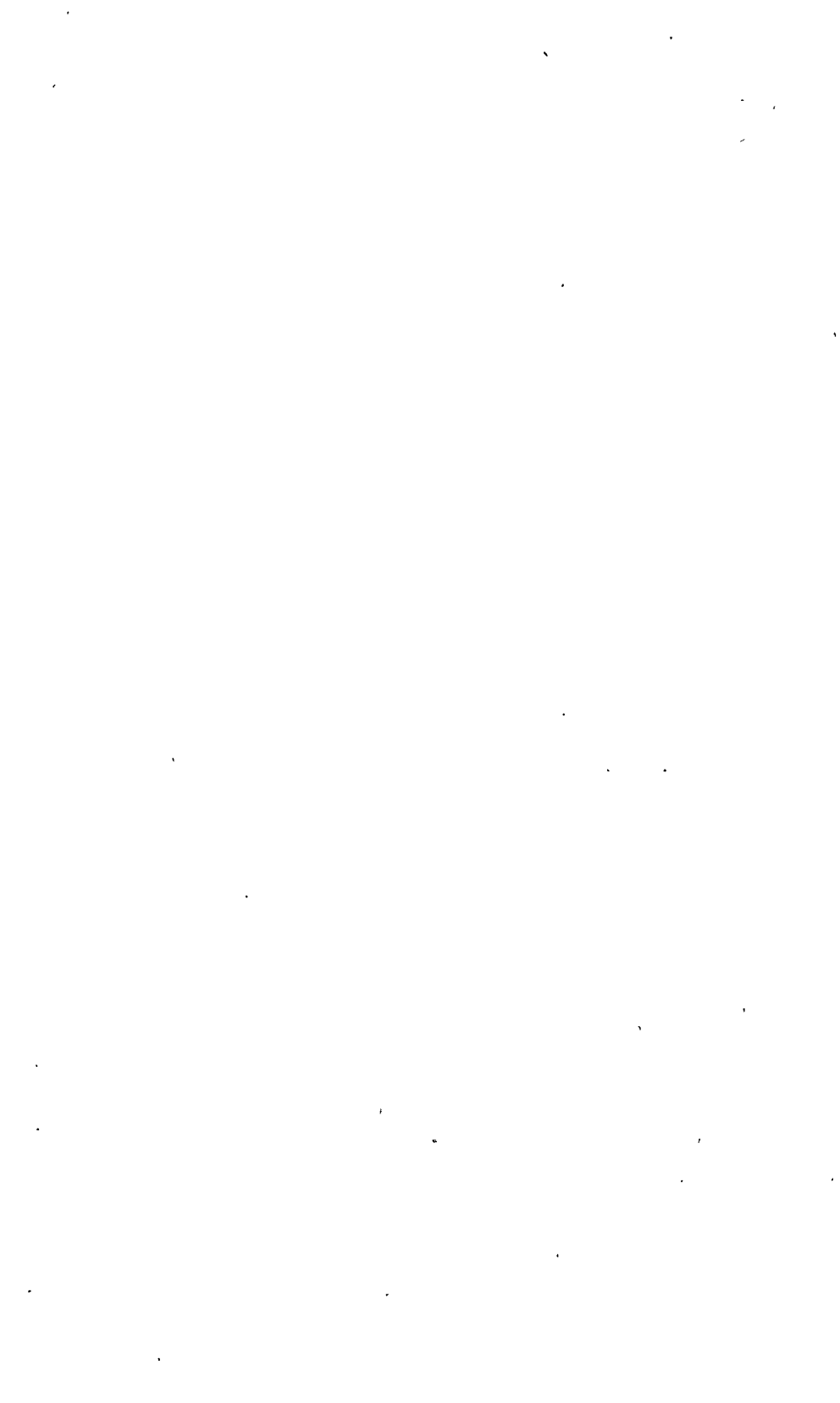
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TABLE OF CONTENTS

IODINE AND MORBUS BASEDOW (EXOPTHALMIC GOITER). Karl Petren, Lund, Sweden	1
ON THE ASSERTED NON-EXISTENCE OF THE AGE INVOLUTION OF THE THYMUS GLAND. J. Aug. Hammar, Upsala, Sweden.....	18
A NOTE ON THE PARATHYROID AND BROKEN BONES. CASE REPORTS. G. H. French, Herrin, Ill.....	25
LATENT DIABETES. Pedro Escudero, Buenos Aires.....	27
BOOK REVIEWS	34
ABSTRACT DEPARTMENT	37
STUDIES ON VIGOR. XVI. ENDOCRINE FACTORS IN VIGOR. R. G. Hoskins, Columbus	97
PSYCHIC TRAUMA IN PATHOGENESIS OF EXOPHTHALMIC GOITER. Israel Bram, Philadelphia	106
STUDIES OF THE THYROID APPARATUS. XLVIII. AGE, SEX, WEIGHT and SEASON AS LETHAL FACTORS IN CONDITIONS OF PARATHYROID AND THYROID DEFICIENCY. Frederick S. Hammett, Philadelphia.....	117
THE ACTION OF ULTRA-VIOLET LIGHT, THYROID AND PARATHYROID SUBSTANCES UPON AN ARTIFICIAL PLASMA IN VITRO. H. W. C. Vines, Cambridge, England	125
STUDIES ON VIGOR. XII. THYROID ADMINISTRATION IN SENILITY. R. G. Hoskins, Columbus	136
STUDIES ON VIGOR. XIII. EFFECTS OF EARLY CASTRATION ON THE VOLUNTARY ACTIVITY OF MALE ALBINO RATS. Howard M. Gans, Columbus... ..	141
STUDIES ON VIGOR. EFFECT OF FRACTIONAL CASTRATION ON THE VOLUNTARY ACTIVITY OF MALE ALBINO RATS. Howard M. Gans, Columbus.....	145
ABSTRACT DEPARTMENT	149
STUDIES ON THYROIDS. Oscar Riddle, Cold Springs Harbor, N. Y.....	161
HOW FAR CAN RECENT STUDIES ON THE OVARIAN FOLLICULAR SUBSTANCE BE APPLIED TO THE HUMAN? A BRIEF DISCUSSION OF THE THERAPEUTIC ASPECTS OF THE PROBLEM. Emil Novak, Baltimore.....	173
CORPUS LUTEUM IN ITS RELATION TO MENSTRUATION AND PREGNANCY. J. P. Pratt, Detroit	195
CLINICAL MANIFESTATIONS OF WATER INTOXICATION IN A CASE OF SEVERE DIABETES INSIPIDUS, WITH SOME NOTES ON THE DISTURBANCES OF BLOOD COMPOSITION AND VASOMOTOR MECHANISM. Albert M. Snell and Leonard G. Rowntree, Rochester, Minn.....	209
THE ACTION OF SUPRARENAL TISSUE UPON LECITHIN. H. W. C. Vines, Cambridge, England	224
VERTIGO AND DEAFNESS ASSOCIATED WITH HYPOTHYROIDISM. Robert C. Moehlig, Detroit	229
THE EFFECT OF PREGNANCY AND LACTATION ON THE BLOOD CALCIUM OF THYROPARATHYROIDECTOMIZED DOGS. E. Larson and N. F. Fisher, Chicago... ..	233
A CASE OF RETINITIS PIGMENTOSA ARRESTED BY ORGANO THERAPY AND ANTISYPHILITIC TREATMENT. H. L. Hilgartner, Austin, and J. L. Lankford, San Antonio	237

ABSTRACT DEPARTMENT	241
SUPRARENAL CARCINOMA WITH PUBERTAS PRAECOX IN A BOY THREE YEARS OF AGE. Murray B. Gordon and E. Jefferson Browder, Brooklyn.....	265
THE RELATION OF CERTAIN GLANDS OF INTERNAL SECRETION TO THE DEVELOP- MENT OF ATHEROSCLEROSIS. Shepard Shapiro, New York.....	279
THE REPLACEMENT OF THE SERUM CALCIUM AND THYROID GLAND IN RABBITS AFTER INTRAVENOUS INJECTIONS OF OXALATE. H. W. C. Vines, Cam- bridge, England	290
STUDIES OF THE THYROID APPARATUS. XLIX. WATER BALANCE IN CONDI- TIONS OF THYROID AND PARATHYROID DEFICIENCY. Frederick S. Ham- mett, Philadelphia	297
THE EFFECTS OF TESTICULAR SUBSTANCE IMPLANTATIONS ON GLUCOSURIA. L. L. Stanley, San Quentin, Calif.....	305
THE INTERSTITIAL CELLS OF LEYDIG IN THE HERMAPHRODITE PIG. A. H. Davis and George T. Pack, Tuscaloosa, Ala.....	313
THE EFFECT OF THYROID EXTRACT UPON BODILY FUNCTION IN HYPOTHY- ROIDISM. Charles H. Lawrence, Boston.....	321
FURTHER STUDIES ON TESTICULAR GRAFTING. W. F. Boukalik and R. G. Hoskins, Columbus	335
FURTHER OBSERVATIONS ON THE DEPRESSOR SUBSTANCE IN LIVER EXTRACT. Theo. C. Burnett, Berkeley.....	338
BLOOD SUGAR CURVES IN DIABETES INSIPIDUS AND IN HABITUAL AND EXPERI- MENTAL EXCESSIVE WATER DRINKING. R. B. Gibson, Elizabeth J. Magers and Herman Dulaney, Iowa City, Ia.....	341
BOOK REVIEWS	348
ABSTRACT DEPARTMENT	351
HEMOCHROMATOSIS. A REPORT OF THREE CASES, WITH RESULTS OF INSULIN THERAPY IN ONE CASE. T. L. Althausen and Wm. J. Kerr, San Francisco	377
THYMIC DEATH. E. Bonilla, Madrid.....	423
THE FIELD OF USEFULNESS OF IODINE IN GOITER. A. F. Jennings and S. W. Wallace, Detroit	431
THE ASSOCIATION OF UROLOGIC LESIONS WITH HYPOTHYROIDISM. Harvey G. Beck, Baltimore.....	438
HEADACHE IN RELATIONSHIP TO OVARIAN DYSFUNCTION. Ernest Clyde Fish- baugh, Los Angeles	445
A NEW (ORBITAL) METHOD FOR EXTIRPATION OF THE HYPOPHYSIS IN THE PIGON. D. Ogata and H. Nishimura, Nagasaki, Japan.....	451
BOOK REVIEWS	461
ABSTRACT DEPARTMENT	463
CARBOHYDRATE METABOLISM IN HYPERTHYROIDISM. Henry. J. John, Cleve- land	497
PATHOLOGY OF GOITER. Arthur E. Hertzler, Halstead, Kan.....	582
ADDISON'S DISEASE WITHOUT PIGMENTATION: REPORT OF A CASE. David G. Ghrist and Leonard G. Rowntree, Rochester, Minn.....	589
A CASE OF PHYSIOLOGICAL CASTRATION IN THE FOWL. H. B. Yocum and J. B. Flynn, Eugene, Oregon.....	593
ABSTRACT DEPARTMENT	597



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ON THE ASSERTED NON-EXISTENCE OF THE AGE INVOLUTION OF THE THYMUS GLAND

J. AUG. HAMMAR

UPSALA

The regressive changes brought about in the thymus gland by transient circumstances, particularly those of nutritive kind, have for more than 250 years far too often been confused with those occurring in the existence of every individual at a certain period of normal development. To what confusion this intermingling of the accidental thymus involution with the age involution of the organ has led is clearly evidenced by the survey of the literature on the subject published elsewhere by the author (Hammar, 1926).

During all this time, however, the existence of the age involution has for all intents and purposes never been doubted. It has been the privilege of the most recent times to create a new phase in the history of scientific mistakes by classing the phenomenon of age involution with the viewpoints of accidental involution.

For such is the essence of the conclusions recently formed by Hammett (1926), when he says that "there is no such phenomenon as the 'age' involution of the thymus, at least before young adulthood after the attainment of sexual maturity"; . . . "puberty is not the initiator of a permanent progressive loss of weight or involution"; . . . "the thymic involution of puberty is simply a reaction to the general physiological disturbance of the period."

It is on the basis of weight determinations of the thymus in rats that the author in question has arrived at these ideas, different from all previous experience. One is immediately struck with the fact that, in drawing his conclusions, the author entirely ignores the really self-evident circumstance, persistently emphasized in recent literature on the thymus, that, from a functional point of view, the noteworthy factor is not to be found in the size of the organ but in the amount and structure of the

parenchyma. About this no mention whatever is made in the above quoted account.

Hammett gives the following picture of normal thymus growth in the albino rat up to young adulthood: "The thymus progressively increases in size up to puberty. Sometime during this period a loss of weight occurs. With the completion of pubertal adjustment growth is resumed and the organ increases in weight. This recovery, however, does not bring the weight of the organ by 150 days of age, back to the value which was reached before the beginning of the pubertally conditioned involution. That it might do so if a longer period was provided under optimum conditions is probable."

It is not the first time that such observations have appeared in the literature concerning the mean variations in weight about the time of puberty, as apparently believed by Hammett. In Gedda's (1921) investigation of the anatomy at different ages of the thymus in the rabbit there are entirely analogous observations. Fig 1 is taken from the figure in his work, the same signs being used. The upper curve represents the average

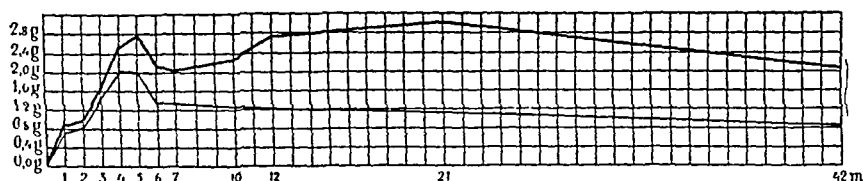


Fig. 1. Average value of thymus weights (heavy line) and of parenchyma weight (light line).

weight of the body of the thymus at different ages. We recognize here the transient post-pubertal reduction of the weight, mentioned by Hammett, accompanied by an increased weight up to the age of 21 months, when it even exceeds that at puberty. Gedda, however, in his material carried out determinations of the parenchyma, and the mean values of the parenchymic weights will be found in the lower curve of the same figure. This curve shows a relatively rapid reduction immediately after puberty, followed by a slower one, but continuous, during the subsequent period of life.

A more detailed interpretation of these conditions will be found in Gedda's Fig. 3, represented here as Fig. 2. It is clear from this that cortex and medulla, separately, have their mean

maximum development occurring at about the time of puberty after which, on the whole, there seems to be a continuous reduction in quantity. *The post-pubertal increase of weight of the organ is entirely due to quantitative increase of the interstitial tissue.*

I have no doubt that Hammett will find similar conditions in his rat-material if he subjects it to an exact, quantitative investigation.

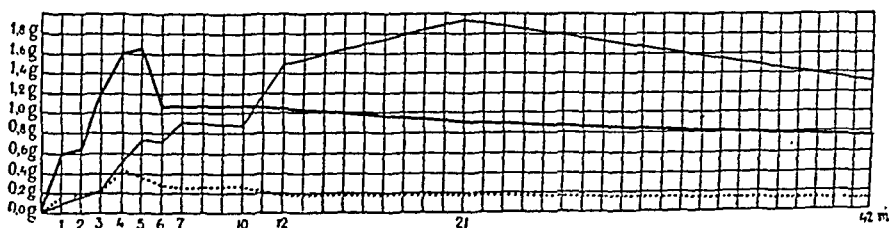


Fig. 2. Average weight of thymus cortex (heavy line), the medulla (dotted line) and interstitial tissue (light line).

The author further says: "The question naturally arises as to whether the pubertal loss of weight is due to a direct influence of the surge in gonadal incretory activity upon the thymus, or whether it is merely a response to the general disturbance incident to the particular stage of development. Since gonadal activity continues for some time after the attainment of sexual maturity it would be expected that if this is the immediate cause of the thymic recession, the latter would continue. But as the data show, this does not happen under close to optimum conditions."

In accepting Hammett's premises, therefore, the conclusion may rightly be drawn, both in respect of rabbit and man—the two mammalian species in which parenchymic determinations have so far been made and for which the average, continuous post-pubertal reduction of the parenchyma has been determined—that "the pubertal loss of weight is due to a direct influence of the surge in gonadal incretory activity upon the thymus," to again quote the author.

Experimental results may now be given in support of such view. If, following the example of Fiore and Franchetti, repeated injections of blood-serum from sexually mature animals of the same species are made into prepubertal animals, involu-

tion of the thymus occurs, while such involution does not take place if the injections are made with blood-serum from animals not sexually mature. In a paper now in press (1927) I have been able to show that the involution in question has not the character of accidental involution but of that of age.

And so I have also touched upon another factor in Hammett's account which has not received attention: it is far from the fact that the pictures of accidental involution and that of age are identical; to determine, therefore, whether one form or the other is present need be no matter of conjecture, as one is led to believe from Hammett's account, where no mention is made of any microscopical examination. The most obvious difference will be found in many cases in the prominent quantitative increase of the interstitial fatty tissue in the thymus in age involution, a condition having no correlation with the accidental involution, because although the interstitial tissue here may be *relatively* increased, it is indeed actually reduced, even if to a less extent than the parenchyma. Another and more important difference between the two involution forms will be found in the fact that in age involution the boundary between cortex and medulla remains well defined still in advanced age, while at the accidental involution this boundary becomes rapidly blurred by a wholesale emigration of lymphocytes occurring, then soon entirely disappearing, giving to the parenchyma an altogether uniform appearance.

The assumption is advanced by Hammett that he has arrived at more exact ideas of the age involution than his predecessors because of the fact that he has studied animals living under particularly satisfactory hygienic conditions: "under close to ideal conditions with respect to diet, environment and health." This is, of course, nothing but good. But the importance of it is evidently over-estimated by Hammett when he says: "There is a general belief that the thymus undergoes a normal 'age' involution, as distinguished from the 'accidental' involution caused by dietary and other disturbances. Exact proof for this belief is lacking. This is because no individual lives a life that is completely free from physiological fluctuations, due to disease or dietary variations, which may well have produced an 'accidental' thymic involution of such degree that complete recovery therefrom has been impossible."

I know of no single fact which justifies the view that the effects of the accidental involution would have such an irreparable character. On the contrary, Jonson's (1909) inanition

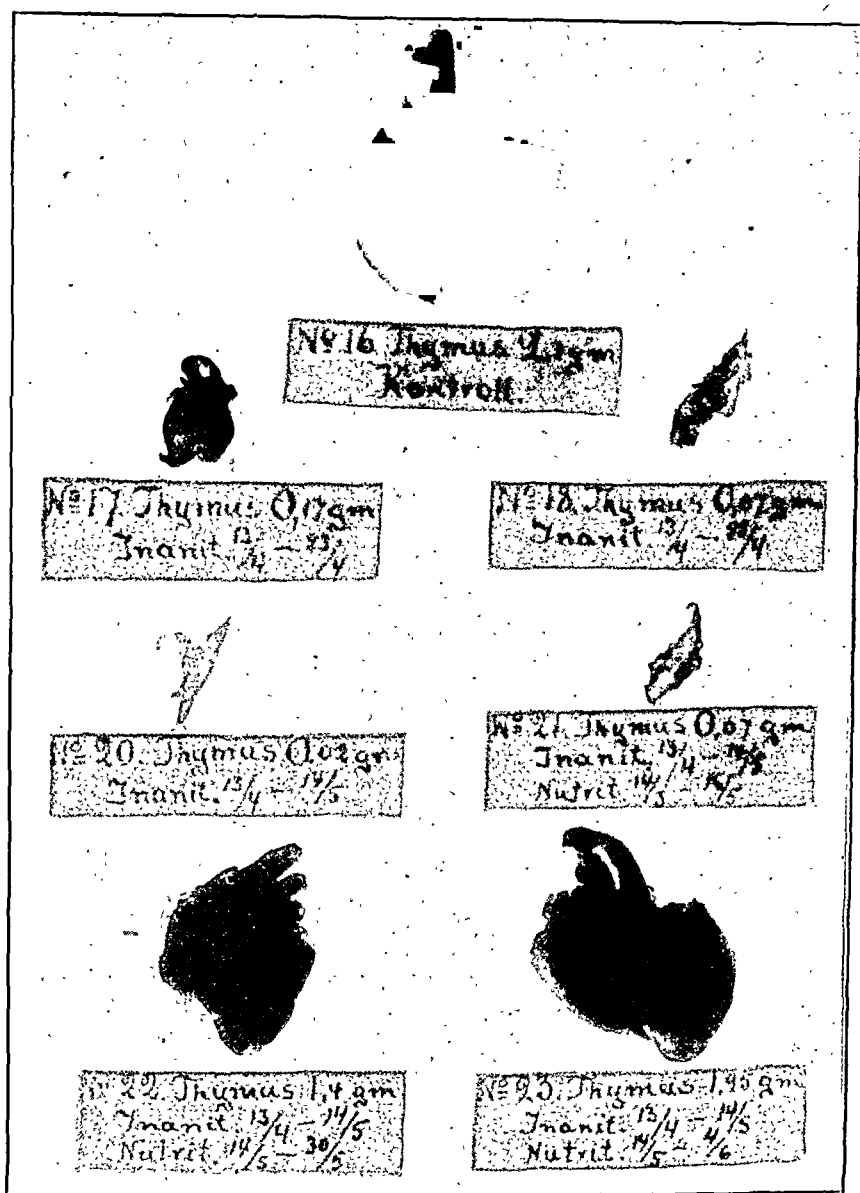


Fig. 3. Photographs of thymus before, during and after inanition, showing marked recovery of size.

experiments give support entirely in the opposite direction; they bear evidence of a surprisingly quick and complete regenerative

power of the organ even when the accidental involutionary process has been driven to extreme. I am taking the liberty of illustrating this by reproducing in Fig. 3 the picture he submitted of the thymus gland from one of his experimental series of regeneration. It is evident from these pictures that even after reducing the weight of the organ down to 1/100th of that of the control animal's by one month's incomplete nutrition, 14 days' full nutrition was sufficient to bring back the size to practically the same as that of the control organ.

If the age involution therefore must be considered as a characteristic process, clearly defined from that of the accidental involution, it must, on the other hand, on no account be looked upon as a separate phenomenon, inexplicable from the point of view of other conditions pertaining to the organ. What is more, it can be conveniently included in that fairly large group of present experiences which bear evidence of how intimately the thymus is dependent upon several of the endocrine organs—besides the gonads, the suprarenals, thyroid, parathyroids, the pituitary body. Indeed, some of Gellin's (1910) experiences seem to indicate that also at the initiation of the age involution other endocrinic organs than the sexual glands may, to some extent, be co-operating.

SUMMARY

The points to which this brief account mainly purports to draw attention are as follows:

That an increase of the mean weight of the thymus after puberty does not exclude the possibility of a simultaneous reduction of the parenchyma;

That, therefore, it is premature to base a denial of the existence of the pubertal age involution upon the post-pubertal increase of the mean weight of the thymus;

That the age involution and the accidental involution present clearly different microscopical appearances and are therefore only confounded when the organic structure is neglected;

That experiments prove that substances with a depressor effect on the thymus circulate in the blood of the sexually mature individual, but are lacking in the blood before puberty; that these substances should originate from the gonads has so far not been definitely proved, even if probable;

That the accidental involution in nutritive disturbances has no definite character but may, under favorable conditions, be followed by a rapid and complete regeneration of the organ;

That the involution occurring normally at puberty is no unique phenomenon but only one phase of the general dependence of the thymus on the endocrinic system or at least several of its organs.

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LATENT DIABETES

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A diabetic who arrives at the physician's office thirsty, glycosuric and hyperglycemic, brings the disease in a completely developed form. It is highly advisable, however, to be able to detect diabetes in the early stages, when there is no sugar in the urine and a normal amount in the blood. This represents the functional period of the disease.

At present it is not difficult to distinguish between renal or "innocent" diabetes and *diabetes mellitus*. The first, not yet well known or understood, is characterized by glycosuria, not accompanied by a rise in blood-sugar content. It is not influenced by decreasing carbohydrate diet and the administration of insulin. The second, *diabetes mellitus* is produced by a derangement of metabolism of the carbohydrates; and it is detected by the appearance of sugar in the urine and an increase above normal of the amount of sugar in the blood. It is influenced by dietetic treatment and the administration of insulin. It occurs in two clinical forms, as the glycosuric and the aglycosuric. The latter I term "hidden diabetes," the principal characteristics of which are an increase of sugar in the blood and an absence of sugar in the urine, with high carbohydrate tolerance—more than two grams per kilo of body weight.

Three clinical forms of "hidden diabetes" are known, indicated by (a) obesity; (b) hypertension or elevated blood pressure without cardiac hypertrophy, and (c) a cutaneous disease, such as eczema, furunculosis or pruritis.

Before giving proofs of the existence of "latent diabetes," I will endeavor to convey my conception of what is known as normal fasting blood-sugar content, and the value of the diagnosis of low carbohydrate tolerance, by means of a food tolerance test.

I have determined in the Argentine by the Foley and Wu method, on young and healthy persons, the normal blood-sugar content after 12 hours' fasting. I consider as strictly normal

a value of 0.80 to 1.00 part per 1000; transition glycemia is indicated when the amount rises to 1.2 parts per 1000, and positive abnormality is evidenced when the latter amount is exceeded.

The fasting hyperglycemia indicates a derangement of metabolism of the carbohydrates. It is not the same with glycemias that I term "Transition glycemias." In order to prove this it is necessary to make a food tolerance test. Many trials were made before the following method was selected: after 12 hours' fasting, and knowing the blood-sugar level, the patient was given a meal of 2 grams of glucose per kilo of body weight. Blood-sugar content was determined three hours later. In the case of a normal person, there is a slight hypoglycemia three hours after the glucose tolerance test, which indicates to me that there has been a normal hyperfunction of the islands of Langerhans due to the transitory hyperglycemia. The following results can be observed:

Case 1: Three hours after the glucose test a hyperglycemia appears, confirming an abnormality in the metabolism of the carbohydrates.

Case 2: There is neither hyperglycemia nor the physiological hypoglycemia three hours after the test. The fasting blood-sugar content was 0.90 part per 1000; three hours after the test it was 0.98. It is thus impossible to affirm or to deny the existence of a derangement of metabolism of the carbohydrates.

To this special case I have devised a food test involving the functional exhaustion of the pancreas, which has been designated the Escudero test for cases of latent diabetes. The procedure is as follows: For ten days the patient receives a daily meal composed of 6 grams of carbohydrates and 1 gram of protein, each per kilo of body weight, and the fat necessary to form a diet sufficient for the age, weight and social conditions. After this, the fasting blood-sugar content is determined and the glucose test is repeated, as already described. Up to the present I have obtained the following results.

1. *Negative:* No rise in blood-sugar content; three hours after the second glucose test the physiological hypoglycemia test exists. In summary it may be said that the condition is the same before and after the test (see Case 11 in the accompanying table).

2. *Uncertain:* The Escudero test does not alter the blood-

sugar content; the glucose test applied subsequently shows no rise, but a disappearance of the normal hypoglycemia (see Case 10).

3. *Positive:* (a) The Escudero test produces a rise in blood-sugar content; there is a fasting hyperglycemia. (See Cases 1, 7 and 9.) (b) The fasting blood-sugar content is the same, but the second glucose test is positive. (See Cases 2, 3, 4, 5, 6 and 8.)

By these means I have proved the existence of a derangement of metabolism of the carbohydrates, but not the existence of a disease. This agreement between the subjective symptomatology by the patient and the inadequate metabolism of carbohydrates is proved by the following facts:

1. During the high carbohydrate diet test the symptoms become more intensive and the patient grows worse.

2. By submitting the patient to a low carbohydrate diet and by administering insulin he recovers completely.

An additional fact should be noted: In spite of normal blood-sugar content, it is possible to inject a relatively high dose of insulin without producing hypoglycemia.

I have recruited patients with "latent diabetes" from those with chronic diseases without clear etiology; and to date I have been unable definitely to define its limits. Many cases belong to different fields of pathology. These are not comparable among themselves but, nevertheless, they have a point of contact: the existence of a particular abnormality of metabolism of the carbohydrates and success in the therapeutic treatment of diabetes.

Before adding a brief description of the important characteristics of the cases under observation, I should like to take the opportunity to discuss the opinions of some authors who have employed the same or similar terms but whose ideas do not coincide with my conception of the disease:

Labbé (1), studying obesity, characterizes the subjects with sugar-free urine and rise in blood-sugar content as "paradiabetics," and says that "this is a border line disease of diabetes, but its transformation into true diabetes has not been proved." Notwithstanding this opinion, I have proved the contrary, and I consider the disease a "hidden diabetes," that is, a hyperglycemia with constant sugar-free urine.

Klauber (2) has reported a case of generalized eczema with an unusually high blood-sugar content and no sugar in the urine. These symptoms in a patient without renal disease are evidence that he is suffering from potential *diabetes mellitus*, in the author's opinion. To my mind, this case and the cited case of Labbé are examples of "hidden diabetes."

John (3), in an important work on "Glucose tolerance and its value in diagnosis," employs the terms "early," "latent" and "pre-diabetic" as synonymous; and in his classification he considers the condition as "weak normal," characterized by "maximum rise is blood-sugar curve from $1\frac{1}{2}$ to $1\frac{1}{2}$ hours after the injection of 100 grams of glucose, the curve returning to the normal level in about 3 hours." In a table this author summarizes 100 cases, with four diagnosed as prediabetic, one of which can be considered as "hidden diabetes," because the fasting blood-sugar content rose to 1.39 parts per 1000. The prediabetic example quoted by John may be considered as the first stage of the disease.

The diseases of the skin, eyes and joints have given me the most characteristic cases, of which I will give a brief description:

Observation 9797—Private Clinic. A girl of 22 years was in perfect health, except for a furunculosis of the face that has resisted scientific treatment for four years. Her blood sugar fasting was 0.93 parts per 1000; three hours after the glucose test it was 1.10. By way of treatment she was given low carbohydrate meals and injections of 10 units of insulin one hour before breakfast. Treatment was continued three months. She made a complete recovery that was still maintained five months after cessation of treatment.

Observation 9954—Private Clinic. A woman, 43 years old, had painful infiltration of five years' duration on both legs. The patient had neither renal, cardiac, nervous disease, nor dilated veins of the legs. Her height was 1.49 meters and her body weight, 71 kilos. Her blood sugar fasting was 1.07 parts per 1000; three hours after the glucose test it was 1.25 parts per 1000; glycosuria was 11 parts per 1000. By way of treatment she was put on a diet consisting of 2 grams of carbohydrate, 1 gram of protein and 1 gram of fat, each per kilo of body weight; 20 units of insulin was given. Complete recovery was reported.

Observation 9724—Private Clinic. A man, 52 years old, whose father was a diabetic, had suffered for 15 years from anthrax. At the beginning of this illness he had attacks every three or four months, but during the last year he had had it constantly. However, it never developed to suppuration, although considerable infiltration resulted and it became larger than a peach. He was attended by many physicians in the Argentine and abroad, and all classes of local and general treatment were tried (including operations and the administration of vaccines), but without result. Sugar was never found in the urine. His stature was 1.76 meters, and body weight, 81 kilos. His blood sugar fasting, 1.08 parts per 1000; three hours before the

glucose test, 0.99 part per 1000. The Escudero test was tried. A daily meal, for 10 days, composed of six grams of carbohydrates, one of protein and one of fat, each per kilo of body weight, was given. This food aggravated the disease, and three anthracotic lesions developed on his leg. Despite this, the fasting blood sugar remained the same (0.96 part per 1000), but a new glucose test was positive (1.16 parts per 1000). The treatment consisted of a low carbohydrate diet with 24 units of insulin per day. A week later one of the anthracotic lesions was arrested, and the third disappeared within 15 days. The patient continued the treatment with good result.

Observation 8107—Private Clinic. A man, 50 years old, whose father was a diabetic, had suffered for six years from ocular rheumatism (*iritis rheumatica*). In the beginning of his illness the attacks occurred every four or five months; at the last they occurred monthly. I saw the patient during the last attack, which lasted for four months. He had been attended by the best specialists in Buenos Aires and had been sent to me in the hope that I could discover a general cause that would explain the case. He suffered continuously, and it was necessary to administer analgesics daily to relieve the pain. The fasting blood-sugar content was 1 part per 1000; three hours after the glucose test it was 0.80. As the test gave a negative result, the Escudero test was tried. After ten days of high carbohydrate diet, the fasting blood-sugar content was found to be 1.5 parts per 1000, confirming the existence of latent diabetes. The patient was treated with low carbohydrate diet and 20 units of insulin daily. From the second day of treatment the pain became tolerable; and at the end of the first week the recovery was complete. The patient has continued the same treatment with excellent results.

Observation 1644—Our Ward. Diagnosis, *prurigo ferox*. The patient had suffered for three years, and the area of itching was general. When he entered the clinic, he was unable to sleep, and it was necessary to administer morphine. On three occasions he attempted to take his life. The skin of the entire body had a dark color; it was coarse and compact and with diffused subcutaneous infiltration. All classes of treatment were tried, but without result. A general examination gave a negative result. Fasting blood-sugar content was 0.9 parts per 1000; three hours after the glucose test it was 0.85. After the Escudero test the second glucose test gave a positive result; from 0.90 to 1.16 parts per 1000. The following treatment was applied: A diet with 2 grams of carbohydrates, 0.75 gram of protein and 3 grams of fat daily, each per kilo of body weight, and 40 units of insulin daily. The result was excellent. The skin became soft, thin and without subcutaneous infiltration; the itching became less intensive; sleep became normal and the patient seemed to acquire a new desire for life. In this case the softening of the skin occurred first, followed by the elimination of the itching.

I believe that the study of derangement of metabolism of the carbohydrates is in its infancy, and that before us stretches a great and unexplored field for research. Regarding latent diabetes, two different interpretations can be submitted: (1) that it is the first stage of *diabetes mellitus*, or (2) that it is a new clinical form of the disease. No doubt, the beginning of *diabetes mellitus* is a functional derangement. In this stage the urine is always free from sugar, and the blood-sugar content is more or less normal. The high carbohydrate food test, according

Cases	Observation Number	BEFORE			AFTER		
		Blood Sugar Per Thousands		Urine	Blood Sugar Per Thousands		Urine
		Fasting	3 Hours After		Fasting	3 Hours After	
1	8017	1.0	0.84	Sugar free	1.57	1.42	Glycosuria fasting 1.50 per 1000 3 hours after 2.20 per 1000
2	1665	0.769	0.74	Sugar free	0.86	0.97	Sugar free
3	1666	1.025	1.	Pathological traces 3 hours afterwards	0.845	1.	Pathological traces 3 hours afterwards
4	1669	0.98	1.025	Sugar free	0.87	1.	Pathological traces 3 hours afterwards
5	1667	0.95	0.94	Sugar free	0.92	1.39	Sugar free
6	1664	0.90	0.85	Sugar free	0.905	1.065	Sugar free
7	9004	1.16	Sugar free	1.40	1.50	Sugar free
8	P. E. 9909	1.08	0.99	Sugar free	0.96	1.08	Sugar free
9	9932	1.03	0.77	Sugar free	1.20	0.76	Sugar free
10	P. E. 1694	1.06	0.97	Pathological traces 3 hours afterwards	0.90	0.93	Sugar free
11	1695	1.11	1.08	Sugar free	0.97	0.95	Sugar free

to my technic, generally produces an increase of sugar in the blood. This form is not really a latent diabetes but the first stage of *diabetes mellitus*—the prediabetes of John.

With the designation "latent diabetes" I desire to refer to a chronic disease that will never become *diabetes mellitus*—a disease characterized by a special derangement of metabolism of the carbohydrates, with urine free from sugar and normal blood-sugar content. The symptoms may vary, and they may or may not resemble the symptoms observable in *diabetes mellitus*, such as itching, anthrax, eczema, subcutaneous infiltrations, joint and muscular pains. The rapid success of the treatment by low carbohydrate diet and insulin demonstrates the relationship between the disease and the derangement of metabolism of the carbohydrates.

This opinion will be contested. It will be said that insulin has been used with positive results in the treatment of diseases other than diabetes, to which I agree. But I maintain that it was not proved that these cases were not instances of latent diabetes. In my ward, and in the study of the disease, I have

found patients not suffering from latent diabetes on whom the insulin treatment produced no result.

The data obtained and the general outcome of my studies and investigations are such that I have felt justified in presenting the results as a contribution to the contemporary knowledge of the study of diabetes; and I trust that my colleagues in the United States will honor me with their interest in my researches with their comments and their criticisms.

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Escudero (P.) and Puchulu (F.): La obesidad como manifestación de la diabetes oculta. Arch. Españoles de enfermedades del Aparato Digestivo y de la Nutrición, 1926, **2**, 531.
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Book Reviews

THE SURGICAL TREATMENT OF GOITER. William Bartlett, 1926.
The C. V. Mosby Company, St. Louis. Pp. 365.

The author's purpose in writing the book is set forth as the presentation of a detailed study of the elaborate procedure involved today in the preparation, operation, and after-cure of the goiter patients who present themselves at the clinic with which he is connected. It is written in the hope that it may appeal to the well-trained young general surgeon who is inclined to broaden his experience in the special field of thyroid surgery. The author frankly refers his readers for many matters of fundamental details to earlier monographs on the same subject.

Three chapters are contributed by other authors: "Pathology," Louis B. Wilson; "The Heart in Goiter," Samuel B. Grant; "Laryngeal Complications," French K. Hansel.

The chapters by the author include such material as would be expected in a book having this title. Perhaps the two most interesting are those on "Unusual Manifestations of Goiter" and "After Treatment." The details of operative technic are set forth fully and clearly.

The book is thoroughly readable throughout. It is well illustrated with 130 figures. Altogether the author has succeeded well in carrying out his declared purpose.

BIOLOGICAL ABSTRACTS. A Comprehensive Abstracting and Indexing Journal of the World's Literature in Theoretical and Applied Biology, Exclusive of Clinical Medicine. Published under the Auspices of the Union of American Biological Societies with the Co-operation of Biologists Generally. Editor-in Chief, J. R. Schramm, University of Pennsylvania, Philadelphia.

The editors' preface states: "The increasing interdependence of the various fields of biological science, coupled with the constantly growing volume and complexity of the literature, have in large part furnished the stimulus for the effort, herewith inaugurated, to provide a comprehensive abstracting and indexing organ for the world's literature in theoretical and applied biology.

BOOK REVIEWS

"The necessity of specialization, probably to an increasing degree, is recognized; on the other hand, it is becoming more and more apparent that highly specialized work is more likely to result in sound progress if undertaken with at least reasonable familiarity with contributory fields. Biological Abstracts will therefore endeavor to provide through its current abstract numbers and annual alphabetic and systematic indexes a guide to the literature conveniently arranged by specialists; at the same time through its comprehensiveness it is hoped it may enable specialists to maintain intelligent contact with related or contributory phases of biology—contacts which in general can be maintained only under some form of abridged reading.

"The development of biological science, in common with other broad intellectual fields, is fundamentally non-nationalistic. The same non-provinciality is vital in its literature guides; therefore, Biological Abstracts will strive to give adequate representation within its field to the literature from all lands. In this effort the widest participation is invited, and is already generously forthcoming, to the end that Biological Abstracts may be the product of a genuine co-operation among biologists throughout the world."

TECHNIQUE IN THE MANAGEMENT OF DIABETIC PATIENTS. Henry J. John, 1927. The William Feather Company, Cleveland, Ohio. Pp. 62.

In acquiring any intricate technic success comes from the mastery of many minor details rather than the general principles. John has offered a little manual setting forth the ways of avoiding the numerous pitfalls in the technic of handling diabetic patients. He discusses briefly and clearly:

- I. The Securing of a Specimen of Blood for Analysis.
- II. Preparation and Intravenous Administration of Glucose Solution.
- III. The Administration of Insulin.
- IV. Transportation of Blood for Blood Chemistry Studies.
- V. A Practical Outfit for Urine Examination.
- VI. Explanation of the Diabetic State.

LA DIABETES Y SU TRATAMIENTO. Mario Quiñones, 1924, Universidad Nacional de Mexico, Facultad de Medicina. Pp. 321.

After brief chapters on the history and etiology of diabetes, Quiñones takes up in detail the treatment of both the adult and juvenile types. The dietary methods of various previous writers are discussed. A section of 80 pages is next devoted to in-

sulin therapy. The third section of the book gives detailed reports of the results of treatment in a series of individual cases. An interesting bibliography of 361 titles closes the volume.

L'INSULINE. Emile Aubertine, 1926. Gaton Doin & Cie., Paris. Pp. 490.

In a volume of nearly 500 pages Aubertin discusses in a lucid way the many topics pertinent to the action of insulin. He takes up seriatim the history, preparation, nature and sources of insulin. Then nine chapters are devoted to an analysis of its action in the body. The third section discusses the practical use of the drug. The catholicity of the author's reading is indicated by the citation of over 1300 articles well selected from the world's literature.

Abstract Department

Epinephrine and blood pressure in dementia praecox and manic-depressive insanity. Backlin (E.), *Acta Psychiatrica et Neurologica* (Copenhagen), 1926, 1, 232; Abst. J. Am. M. Ass., 88, 616.

Using Csepai's technic, Backlin injected 0.01 mgm. of epinephrine intravenously into fifty-eight dementia praecox and ten melancholia patients. In 21% of the dementia praecox cases there was a vagotonic reaction; i. e., an initial decrease of the blood pressure or a retarded, slight increase. In dementia praecox connections were not observed between the intensity or type of reaction and the type or duration of the psychosis or age of the patient. In every case of melancholia a vagotonic reaction was obtained. By administration of atropine and a potassium salt it was possible in some cases to transform the vagotonic into a sympatheticotonic reaction.

Suprarenal insufficiency. Banting (F. G.) & Gairns (S.), *Am. J. Physiol. (Balt.)*, 1926, 77, 100-113; Blood and urine findings in desuprarenalized dogs. Lucas (G. H. W.), *Ibid.*, 114-125.

A detailed study of the symptoms, pathological histology, survival factors, treatment, blood and urine chemistry in suprarenalec-tomized dogs. In 16 animals, both organs were removed at one operation, while in 37, two operations were performed with intervals of 10 days to 6 weeks intervening. In the first group the period of survival varied from 8 to 58 hours with the exception of one animal which survived 388 hours. In the second group, the survival period varied from 50 to 238 hours. In animals surviving less than 50 hours the symptoms noted were partly due to operative shock. In those surviving for longer periods shock symptoms were not observed; in these animals, some time before death the following symptoms were noted: progressive increase in pulse, respiration and temperature at first, inflammation of the margins of the gums, suppression of urine, loss of appetite, weakness, pupil dilatation, drowsiness, vomiting, diarrhoea, loss of consciousness, slower respiration until just before death; temperature below normal, the blood became thick and dark and not sedimenting rapidly. Of methods of treatment tried, it was found that epinephrin and beef cortex extract were ineffective, while intravenous injections of

glucose, extract of dog suprarenal cortex, normal dog serum, and saline injections all prolonged the life of the animals. Protein diet shortened the period of survival. The reader is referred to the original article for the details of autopsy findings, which indicated accumulation of toxic products. Concentration of the blood produced an increase in total N and total solids, Ca and P. Cholesterol and creatinine contents were not appreciably affected; non-protein N was greatly increased, which the authors consider a terminal phenomenon; blood chlorides suffered a decided decrease which was correlated with the increase in Ca and P. The histamine content of the liver seemed to be increased slightly. Urinalyses indicated ability of the kidneys to excrete nitrogenous and inorganic materials at all times.—C. I. R.

Studies on the physiology of the liver. II. Effect of adrenalin upon blood sugar following ligation of the hepatic artery. Collens (W. S.), Shelling (D. H.) & Byron (C. S.), *Am. J. Physiol.* (Balt.), 1927, 79, 689-693.

Adrenalin does not influence the blood sugar level when administered during the hypoglycemic state resulting from exclusion of the arterial supply of the liver. The blood sugar does not necessarily indicate the amount of glycogen present in the organism, since animals on the verge of hypoglycemia but still maintaining a normal blood sugar level may fail to respond to adrenalin with an increased blood sugar level. The failure is not due to a disturbance produced by ligation, but rather to the absence of glycogen from the tissues.—Authors' Abstract.

The effect of forcing fluids, upon survival after bilateral epinephrectomy. Corey (E. L.), *Proc. Soc. Exper. Biol. & Med.* (N. Y.), 1926, 24, 206-207.

The life span in cats after the removal of the second adrenal is sixty hours. This can be doubled or trebled by giving large quantities of certain watery fluids to the operated animal by a stomach tube. Ringer's solution, 1% sodium chloride, sodium bicarbonate and 5% glucose prolonged life. Sodium acetate had no influence.—J. C. D.

The effect of forcing fluids upon survival after bilateral epinephrectomy. Corey (E. L.), *Am. J. Physiol.* (Balt.), 1927, 79, 633-640.

The oral administration of large quantities of fluid to bilaterally epinephrectomized cats prolongs life. Solutions of certain substances (i. e., glucose, NaCl, etc.) are more effective than others in maintaining the animal in a normal condition. The explanation why forcing fluids prolongs the life of double operated cats is not

entirely clear. It seems to partially relieve the dehydration which is not one of the train of symptoms of adrenal insufficiency in cats, and possible by the consequent diuresis flushes toxic substances out of the organism.—Author's Abstract.

Action of cortical extract of suprarenal. Fujii (M.), Japanese Jour. Pharmacol. (Kyoto), 1926, 3, 1-6; Abst. J. Am. M. Ass., 88, 764.

Fujii summarizes his observations as follows. Intravenous injection of cortical extract of suprarenal causes a fall in blood pressure and augmentation of the respiratory movements in rabbits. The small intestine is stimulated, showing increase in tonus and augmentation of pendulum movements. These actions are considered to be the result of the stimulant effect of the extract on parasympathetic nerve endings. The extract does not have a marked toxicity on mice.

The action of adrenalin in aplastic anaemia. Gibson (G. A.), Lancet, (Lond.), 1926, ii, 948.

Gibson reports marked improvement in a case of very severe aplastic anaemia of unknown etiology following daily injections of adrenalin. Despite the admitted fact that such anaemias are prone to spontaneous improvement, the precarious condition of the patient and the improvement within a week of the beginning of medication leads the author to attach considerable importance to the evidence submitted.—R. G. H.

Functions of the adrenals (Contribution a l'etude des fonctions des surrenales). Gley, Pierre, Paris, 1925, pp. 30.

Three different experiments concerning the function of the suprarenal glands are reported. Using an electrical method for measuring neuro-muscular irritability (chronaxie) in the frog, the author fails to find evidence of an intoxication or curarization action as postulated by Langlois. In the frog and rabbit no evidence of paresis or paralysis has been observed following suprarenalectomy. In attempting to determine the chemical source of adrenalin in the body a known amount of adrenal pulp made from the fresh gland of the horse was mixed with tyrosine and other substances similar in chemical structure. The amount of adrenalin was then determined by the colorimetric method of Abelous based on the oxidation of adrenalin by iodine. These substances were found not to increase the amount of adrenalin. Using both the iodine and physiological (blood pressure) methods, muscle extract was found to increase immediately the amount of adrenalin in fresh suprarenal pulp when the two were mixed. This action is not enzymatic. It was found to be due to the creatine and creatinine content of the muscle extract. A detailed description of the iodine colorimetric

method is given; also critical comparison with the physiological method and Folin's Phosphotungstic acid method. A case of extreme hypertension without other complications at autopsy exhibited enlarged adenomatous suprarenals. The glands were found to contain $1/5$ the normal amount of adrenalin. Two hypotheses are suggested to explain the hypertension, but no conclusion drawn.

—R. R. Durant.

Effects of injections of secretin (Effets des injections de sécrétine).

Hermann (H.), *Rev. Française d'Endocrinol.* (Par.), 1926, 4, 381-415.

In experiments on dogs it was discovered that secretin as ordinarily prepared gave rise to a wave of hyperglycemia. This was not related to the effect on the external secretion of the pancreas. When the extract was purified of its hypotensive constituents the hypoglycemic effect disappeared. When the adrenals were removed the hyperglycemia was not demonstrable. By cross-circulation experiments it was shown that the injection of the hypotensive extract led to secretion of adrenalin.—R. G. H.

The influence of extirpation of the adrenals on the work-capacity of muscle (Der Einfluss der Nebennierenextirpation auf die Arbeitsfähigkeit des Muskels). Hirase (K.), *Arch. f. d. ges. Physiol.* (Berl.), 1926, 212, 582-586.

After removal of the adrenals by thermo-cautery, frogs lived on the average 36.5 hours. Isolated calf-muscles showed fatigue somewhat more rapidly and a somewhat smaller capacity for work, but the difference was too small to draw certain conclusions as to the influence of adrenaline on muscle function.—A. T. C.

Influence of insulin upon the secretion of adrenalin (Influencia de la insulina sobre la secreción de adrenalina). Houssay (B. A.), Lewis, (J. T.) & Molinelli (E. A.), *Compt. rend. Soc. de biol.* (Par.), 1924, 91, 1011.

In these experiments the variations of adrenal secretion during insulin hypoglycemia were studied. Chloralosed dogs were used with adrenal and jugular veins anastomosed according to the technique of Tournade and Chabrol. Glycemia was recorded in both dogs every 15 minutes, two or three times before the transfusion, during transfusion and two or three times after it, following the method of Folin and Wu. In 5 experiments, simple transfusion during an hour did not raise the recipient's glycemia higher than 0.25 grams per 1.000. In 8 experiments the donor (dog) received intravenously 3 clinical units of insulin. An hour after anastomosis was effected and the donor's glycemia varied, during 60 minutes, from 0.3 to 0.4 per 1.000. In these conditions, in 7 cases out of

8, the recipient's glycemia was markedly increased (0.64, 0.47, 1.90, 3.00, 0.29, 0.61, 0.39 grams per 1.000 above the initial amount), the average being 0.812 per 1.000. Hyperglycemia is not produced in the recipient if the donor's glycemia does not fall below 0.5 per 1.000. Preventing hyperglycemia in the donor by means of injections of glucose, the recipient does not show hyperglycemia. After the section of the donor's great and small splanchnic nerves the recipient's glycemia descends very much with insulin (0.19 to 0.33 per 1.000), but the donor's does not rise (7 experiments). To obtain an increase of glycemia of 0.9 per 1.000 it is necessary to inject 0.005 mgm. of adrenalin per kgm. per minute during an hour (slow jugular injection in 60 cc. of physiological solution to chloralosed dogs). In short, insulin hyperglycemia causes a rise of adrenal output by the stimulation of the adrenal secretory centers.—E. A. Molinelli.

Liberation of adrenalin produced by puncturing or electrically exciting the medulla (*Papel de la liberación de adrenalina producida por la picadura o la excitación eléctrica del bulbo*). Houssay (B. A.) & Molinelli (E. A.), *Compt. rend Soc. de biol. (Par.)*, 1924, 91, 1045.

The increase of adrenalin produced by puncturing the medulla has been a matter of much discussion. In 1919, Houssay showed that puncturing the medulla increased adrenal secretion. These experiments proved: that this effect is wanting if the lumbo-capsular veins are clamped before the puncturing; if the clamps are removed and the medulla again punctured, the leg is constricted anew; if the medulla is punctured, the lumbo-capsular veins being clamped, the blood pressure in the arteries is raised but the leg is not constricted, but if the clamps are removed a minute after the puncture, the reaction is produced. (Dogs with bilateral vagotomy, artificial respiration, medullary section at the level of the 11th, 12th spinal vertebrae.) Carrasco-Formiguera, Stewart and Rogoff and others have criticised these experiments. They keep silent over the three first factors, which are the most important, while they criticise the fourth. This one is valuable solely when it is associated with the three first. In the new experiments of Houssay and Molinelli chloralosed dogs were used, following Tournade and Chabrol's adrenal-jugular vein anastomosis. Bilateral vagotomy and artificial respiration were carried out in the donor. In most of the experiments, puncture or electric stimulation of the medulla produced a strong adrenal discharge manifested from 20 to 45 seconds in the recipient by: rise of arterial pressure and increase of the amplitude of the pulsations; vaso-constriction of one of the hind legs, denervated; vaso-constriction of the kidney; vaso-constriction of the spleen; acceleration of the denervated heart; inhibition (or increase) of the movements of the intestine; dilation of the denervated pupil (after

removal of the upper cervical ganglion of the sympathetic nerve and of the ophthalmic ganglion). The section of the donor's great splanchnic prevented the appearance of these effects in the recipient. It cannot be attributed to "redistribution" because the stimulation of the other great splanchnic (the homologous adrenal being removed) causes a rise of the blood pressure in the donor and no noticeable discharge in the recipient. The adrenal output produced by puncturing or stimulating electrically the donor's medulla is capable also of raising the recipient's glycemia. Glycemia was registered twice before the transfusion, then the animals were anastomosed and the donor's medulla punctured. The dosages were made each 15 minutes with 1 cc. of jugular blood, following the method of Folin and Wu. Simple transfusion for $\frac{1}{2}$ to 1 hour, without puncturing the donor's medulla, increased the recipient's glycemia very little if at all. In eight puncture experiments hyperglycemia was obtained four times in the donor (0.40, 1.13, 0.93, 0.81 grams per 1.000) and five times in the recipient (0.47, 0.49, 0.94, 0.26, 0.50 grams). In two instances the glycemia was not raised either in the donor or in the recipient after the puncture. These experiments have no value at all. After the electric stimulation of the medulla four positive results were obtained in the donor (0.46, 0.60, 0.29, 0.33, 0.25 grams per 1.000). There were two negative experiments in both dogs. These experiments show that puncture of electric stimulation of the medulla produces a rise of adrenal discharge. The effects produced are due to a double nervous and humoral mechanism.—E. A. Molinelli.

Reflex secretion of adrenalin. I. (Secreción refleja de adrenalina).

Houssay (B. A.) & Molinelli (E. A.), *Compt. rend. Soc. de biol. (Par.)*, 1924, **91**, 1056.

The experiments were made upon chloralosed dogs with adrenal-jugular vein anastomosis effected according to the technic of Tournade and Chabrol (the vagi were cut and the animals were under artificial respiration). Stimulation of the central end of a sciatic nerve of the donor did not clearly influence the recipient. Strong faradaic stimulation of the central end of a vagus nerve produced adrenal discharge, while in the recipient there was a rise of arterial pressure, rise of the amplitude of the heart beats and vasoconstriction of a denervated hind leg. Stimulation of the two central ends of the vagus nerve at the same time resulted in a greater discharge. Diminution of adrenal secretion as described by Cannon and Rapport was not observed when stimulating the central end of a vagus nerve. This is perhaps due to the fact that the intensity of the current may have been different.—E. A. Molinelli.

Reflex secretion of adrenalin. II. (Secreción refleja de adrenalina).
Houssay (B. A.) & Molinelli (E. A.), *Compt. rend. Soc. de biol. (Par.)*, 1925, **93**, 881.

Stimulation of the central end of the vagus nerves in dogs with denervated heart and liver produces initial, inconstant bradycardia, little marked during 10 to 20 seconds; acceleration of the heart rate (average 30 beats per minute) from 1 to 8 minutes; frequent diminution of the heart beats (late bradycardia) a little below the initial amount at 4 to 5 minutes. Upon clamping the lumbo-capsular veins acceleration is not obtained or else it is slight in most cases. It recurs after removing the clamps. Removal of the suprarenals does not prevent the appearance of initial and late bradycardia. The same phenomena are observed in stimulation of other nerves. The average acceleration for the brachial nerves was 10 beats per minute and for the sciatic, 16 beats. It also depends on reflex adrenal secretion.—E. A. Molinelli.

Discharge of adrenalin produced by muscular activity (Descarga de adrenalina provocada por la actividad muscular). Houssay (B. A.) & Molinelli (E. A.), *Rev. Soc. Arg. Biol. (Bs. Aires)*, 1925, **6**, 125; *Compt. rend. Soc. de biol. (Par.)*, 1925, **93**, 884.

The increase of adrenal secretion during muscular activity has been investigated by two biological tests: glycemia and acceleration of the denervated heart. 1, Effect on glycemia. Chloralosed dogs were used, anastomosed according to the method of Tournade and Chabrol. The sciatic and crural nerves of the donor were cut and the two peripheral ends of the sciatic nerve were stimulated with a tetanizing faradaic current. Every 50 seconds the current was interrupted for 10 seconds. The stimulations lasted half an hour, as did the transfusion. Glycemia was registered following Folin and Wu's method, every fifteen minutes before, during and after the transfusion. There was no increase of glycemia in the donors. Glycemia in the recipients was not increased in such a manner as to show a definite glycemic influence of the suprarenals. 2, Muscular tetanization during 5 consecutive periods of 50 seconds each, with 10 seconds' interval, produced acceleration of the denervated heart (bilateral vagotomy and removal of the stellate ganglia), 5 times out of 9 experiments; the maximum was 12 per minute, and the average 4.5. The former corresponds to a sharp jugular injection of 0.003 mgm. of adrenalin; the latter to 0.0015 mgm. Stimulation of the posterior end of the medulla (section at the level of the second lumbar vertebra), produced better results on account of having tetanized a greater portion of the muscle. The acceleration was: minimum 6, maximum 60, average 15 heart beats per minute. To obtain identical acceleration it is necessary to inject adrenalin sharply and intravenously 0.002 mgm. and 0.004 mgm.

respectively in dogs of that size. The acceleration begins in from 25 to 30 seconds. A slight bradycardia can be seen in the first minute and a late one from 2 to 5 minutes after the close of the stimulation. Exclusion of the suprarenals by tying the suprarenal veins and section of the great splanchnic nerves or removal of the glands, prevents acceleration when the sciatic nerves or the medulla are stimulated anew.—E. A. Molinelli.

Discharge of adrenalin by injection of various substances in the suprarenal (*Descarga de adrenalina por inyección de diversas sustancias en la suprarenal*). Houssay (B. A.) & Molinelli (E. A.), *Rev. Soc. Arg. Biol. (Bs. Aires)*, 1925, 1, 547; *Compt. rend. Soc. de biol. (Par.)*, 1925, 93, 1133.

The experiments were made with the technic of adrenal jugular vein anastomosis of Tournade and Chabrol. Injection in the suprarenal of 0.1 cc. of physiologic solution of normal horse serum does not produce adrenal discharge. A considerable output is obtained upon injecting nicotine (0.0001 mgm.), eserine (0.002 mgm.), hydrastinine (0.001 mgm.), adrenalin (0.025 mgm.), pilocarpine (0.001 mgm.) and morphia (0.01 mgm.). Greater doses of arecholine, acetylcholine, quinine, atropine and strychnine produce an effect. The effect was scanty when using Witt's peptone, veratrine, picrotoxine, and serpent's venom. Strophantine, ergamine, and scorpion's venom had almost no effect. The most active substance was nicotine.—E. A. Molinelli.

Hypothalamic center for adrenal secretion (*Centro adrenalino secretor hipotálamico*). Houssay (B. A.) & Molinelli (E. A.), *Compt. rend. Soc. de biol. (Par.)*, 1925, 93, 1454.

Experiments were made with dogs, following Tournade and Chabrol's technique of adrenal-jugular vein anastomosis. A vertico-frontal incision was made in the donor's cerebrum, directly through the tuber cinereum or infundibulum, 2 or 3 mm. behind the posterior edge of the optic chiasma. Stimulation of the high and medial zone of the incision did not provoke adrenal discharge. Stimulation of the lowest portion, at the level of the infundibulum, produced a well marked adrenal discharge (5 experiments) giving in the recipient a rise of arterial pressure (54; 140; 35; 48 and 80 mm. Hg.), and increase of the rate of the denervated heart (18, 78, 16, 6 and 30 beats per minute). The rise of arterial pressure lasted for 8 minutes. The discharge may be equivalent to 0.015 mgm. of adrenalin. Section of the splanchnic nerves prevents the appearance of these effects. The discharge observed is not due to diffusion of the current, for if an incision is made posteriorly at the level of the protuberance and the flap is applied again, stimulat-

ing the infundibulum anew, no discharge takes place.—E. A. Molinelli.

Concentrated salt solutions causing adrenal discharge (Descarga de adrenalina por acción de sales concentradas). Houssay (B. A.) & Molinelli (E. A.), *Rev. Soc. Arg. Biol. (Bs. Aires)*, 1925, 1, 593; *Compt. rend. Soc. de biol. (Par.)*, 1925, 93, 1456.

Experiments were made on six dogs, using Tournade and Chabrol's technic of adrenal-jugular vein anastomosis. Injection of 2 to 5 cc. of sodium carbonate (5%) in the central end of the carotid artery of the donor produced a marked adrenal discharge which raised the arterial pressure of the recipient (40; 120; 160 mm. Hg.) and accelerated the denervated heart (4; 14; 72 and 92 pulsations per minute). The discharge may be equivalent to 0.0015 mgm. of adrenaline. Citrate of sodium, ammonium, calcium and potassium chloride in 10% concentration injected intravenously and rapidly produced a slight adrenal discharge. Previous section of the splanchnic nerves prevented the appearance of these effects.—E. A. Molinelli.

Anaphylaxis and adrenalin discharge (Anafilaxia y descarga de adrenalina). Houssay (B. A.) & Molinelli (E. A.), *Rev. Soc. Arg. Biol. (Bs. Aires)*, 1925, 1, 661; *Compt. rend. Soc. de biol. (Par.)*, 1925, 93, 1638.

The experiments were made with dogs anastomosed following Tournade and Chabrol's method. Relations between anaphylaxis and adrenal secretion were studied from two points of view; local anaphylactic shock by injecting from 0.1 to 0.15 cc. normal horse serum in the donor's suprarenal. If the animal has been sensitized there is adrenal discharge (4 cases out of 5) that may last from 4 to 20 minutes. Anaphylactic shock was produced in the donor by injecting horse serum intravenously. From 5 to 8 minutes after a slight adrenal discharge was observed. The donor's pressure almost always rose.—E. A. Molinelli.

Amyloidosis of the adrenals as a cause of Addison's disease. Hunter (W. C.) & Rush (H. P.), *Ann. Clin. Med. (Balt.)*, 1926, 5, 404-412.

Amyloidosis of the adrenals of sufficient degree to bring on Addison's disease is apparently quite rare. Four definite and two doubtful instances have been found in the literature, to which is added another showing most of the cardinal symptoms of the Addisonian syndrome. Of particular interest clinically was the multiplicity of symptoms referable to different organs and systems. Extensive active pulmonary tuberculosis and marked renal insufficiency were very evident. The latter proved to be due to amyloidosis of

the kidneys with an accentuation of insufficiency due to some acute infection as shown by marked parenchymatous degeneration. In addition the patient also exhibited very definite signs and symptoms of Addison's disease. Clinically amyloidosis as the etiologic factor producing adrenal insufficiency is not to be differentiated by any methods now available. The common causes of Addison's disease are tuberculosis, syphilis and tumors of the adrenals, and in these conditions the deposition of amyloid is a common occurrence. The lesion itself and not the by-product, amyloid, is the cause of the disease in the greatest percentage of cases. Previous studies, and the one herein reported, have shown a peculiar localization of amyloid in the suprarenals. The deposition is chiefly in the zona fasciculata and reticulosa, to a lesser extent in the zona glomerulosa, and least of all in the medulla. It forms, as in other parts of the body, in the subendothelial spaces and between cells. Amyloid is frequently found in the adrenals when it is present in other organs, but often in only small amounts. It is then readily overlooked or mistaken for hyalin degeneration unless specific stains are employed for its recognition. In cases of Addison's disease which at autopsy reveal apparently healthy suprarenals amyloid should be considered as a possibility, even though rare, and searched for before placing the case in the class of Addison's disease without histological changes in the adrenals.—Authors' Abstract.

Comparative histology and embryology of the adrenals of mammals and man (*Zur vergleichenden Histologie und Embryologie der Nebenniere der Säuger und des Menschen*). Kohno (S.), *Ztschr. f. Anat. u. Entwicklungsgesch.* (Berl.), 1925, **77**, 419-480.

Numerous mammalian species were studied histologically. The embryological work, however, was confined mostly to man, mouse and rat. The human material ranged from 2.8 mm. embryos to children two years old. Special neurological methods were used and the intimate relation of nerve fibers to the medullary cells is discussed from the functional point of view. The vascular relations are briefly discussed. Mammals are divided into two groups depending upon the relative degree of development of the medullary substance at the time of birth. Enormous variability in the amount of lipoids present in the cortical cells is noted, there being apparently none in *Tragulus*. The functional aspect of most of the morphological details are considered.—A. T. R.

Experiments on the hormone action of the adrenal cortex (*Untersuchungen zur Hormonwirkung der Nebennierenrinde*). Kühl (G.), *Arch. f. d. ges. Physiol.* (Berl.), 1927, **215**, 277-290.

Through tracings of the curves of respiration and of muscular contraction of the living adrenalectomized animal, the onset of

adrenal insufficiency can be definitely determined and followed, and the method therefore permits exact experiments on the action of the internal secretion of the adrenal cortex. Injection of adrenine-free cortex extracts is sufficient to delay for hours the onset of the two chief symptoms of adrenal collapse, muscular adynamia and respiratory disturbance. Adrenine, extracts of other organs, glucose, etc., do not produce this effect, so that the extract of the cortex contains a specific internal secretion.—A. T. C.

A new case of sudden death of suprarenal origin not diagnosed (Un nuevo caso de muerte súbita de origen suprarenal no diagnosticado). Marañón (G.), Comas, & Lopez (V.), Arch. d. med. Cirugía y Especialidades (Madrid), 1926, 9, 393.

A patient of 35 years with a positive Wassermann and evidence of gonorrhea, but no suprarenal symptoms, received 6 intramuscular injections of bismuth in the course of 2 months and 6 injections of "lacto-gono" of varying dosage. The patient developed convulsions and died. At autopsy one of the suprarenals was found to be destroyed and the other affected by inflammation. We have, therefore, in this patient a latent suprarenal insufficiency with a tubercular lesion. This condition caused death when aggravated by the vaccine treatment.—E. B.

The adrenaline function of the adrenals in diphtheria poisoning. Molinelli (E. A.), Rev. sud-americana endocrinol.-immunol. quimioterap., 1926, 9, 902-924; Abst., Chem. Absts., 21, 769.

Rats are very sensitive to diphtheria toxin in the first 21 days after adrenalectomy; 30-90 days after the operation the original or even a higher resistance is reached. Dogs deprived of the adrenal medulla are at least as susceptible to diphtheria toxin as normal ones. Diphtheria toxin produces only congestion of the adrenals without increase in weight. The adrenaline content is often but not always diminished. The rate of adrenaline secretion is unaltered; in 25% of the cases it was increased. Diphtheria toxin reduces the adrenaline secretion following splanchnic stimulation and the hypersecretion caused by nicotine. The symptoms of severe diphtheria intoxication cannot be attributed to adrenaline deficiency. Adrenaline or whole adrenaline extract is indicated in severe diphtheria poisoning.

Massage of the suprarenal capsules. Rossello (H.) & Benatti (D.), Ann. Facult. di Med. de Montivideo, 1926, 7, 292-302.

The massage of the suprarenal capsules in the dog caused discharge of adrenalin and a tonic effect on the heart (confirming results of experiments of Popielski and Gautrelet). The authors pro-

pose the use of this procedure in cases of collapse during abdominal operations.—Authors' abstract.

Hypoglycaemia by adrenalin. Rossello (H.) & Rodriguez (E.), *Rev. Soc. Argentina di Biol.*, 1926, **2**, 228.

That adrenalin may sometimes cause a decrease of the blood sugar, or a double phase of hyper- and later a hypo-glycaemia (diphasic action), has been shown by Zondek, Kylin, Dressel and others. The authors relate 35 observations in patients with tuberculosis who had been injected with $\frac{1}{2}$ mgm. of adrenalin (P.D.). In the majority of the patients hyper-glycaemia was observed, while hypo-glycaemia was observed in some, and others a double phase hyper- and later hypo-glycaemia occurred. No relation was seen between reactions and degree of tuberculous involvement.—Authors' abstract.

Blood changes following bilateral epinephrectomy in cats. Swingle (W. W.), *Proc. Soc. Exper. Biol. & Med. (N. Y.)*, 1926, **24**, 208-210; **The acid-base equilibrium of epinephrectomized cats.** Swingle (W. W.) & Eisenmann (Anna J.), *Proc. Soc. Exper. Biol. & Med. (N. Y.)*, 1926, **24**, 212-213.

The author summarizes his work and concludes that one of the causes of death in these animals is the slow accumulation of acid end products of metabolism in the blood due to an inability of the kidney to eliminate them in the absence of the secretion from the adrenal cortex.—J. C. D.

Studies of the functional significance of the suprarenal cortex. I. **Blood changes following bilateral epinephrectomy in cats.** Swingle (W. W.), *Am. J. Physiol. (Balt.)*, 1927, **79**, 666-677.

The blood of unilaterally and bilaterally epinephrectomized cats was analyzed for phosphorous, calcium, sodium, proteins, total nitrogen, non-protein nitrogen, urea and sugar (7 to 14 animals in various cases). Significant increases in phosphorous, protein, non-protein nitrogen and urea were found in the doubly operated animals. The blood sugar decreased (12 cases) to the level at which convulsions occur in insulin injected cats. The blood became concentrated, thus accounting for the rise in protein and total nitrogen. The urine output was diminished and albumin appeared. Slight pathological changes were found in the kidneys. The suggestion is made that death following adrenal removal may possibly be due to either hypoglycemia or acid intoxication, since both phenomena are invariably noted. The hypoglycemia can be corrected by glucose injections, but the animal eventually dies with symptoms of acid intoxication. The acidosis appears to be due to failure of

the kidney to eliminate acids properly, and is of the same general nature as that occurring in certain types of chronic nephritis.

—R. G. H.

Studies of the functional significance of the suprarenal cortex. II. The acid-base equilibrium of epinephrectomized cats. Swingle (W. W.) & Eisenman (Anna J.), *Am. J. Physiol. (Balt.)*, 1927, **79**, 679-687.

Heart-blood obtained from cats which had recovered from unilateral adrenalectomy was compared with that obtained after removal of the second adrenal gland. The blood serum was analyzed for the various acid ions, pH, and total base. Consistent differences following bilateral adrenalectomy were: a fall in pH, carbon-dioxide tension, serum bicarbonate, and total acid; indications of an uncompensated non-volatile acidosis. This seemed to be due to an increase of phosphoric and organic acids. Protein also rose, suggesting inspissation of the serum.—Authors' Abstract.

Morphology of the suprarenal cortex after castration, experimental cryptorchidism and implantation of heterologous gonads in guinea pigs (Das morphologische Verhalten der Nebennierenrinde nach Kastration, künstlichem Kryptorchismus und Implantation heterologer Keimdrüsen beim Meerschweinchen). Takechi (K.), *Ztschr. f. Konstit. (Berl.)*, 1926, **12**, 247-269.

Castration of half-grown animals resulted in a relative decrease in the growth of the suprarenal cortex so that the ratio of medulla to cortex became 1:4 instead of the normal ratio of 1:5. In full-grown animals the siderophil granules of the cortical cells disappear and many pigment granules are formed by three weeks after castration. The decrease in the cortex is largely due to a loss in pars reticularis which normally constitutes about $\frac{1}{3}$ of the cortex whereas in the experimental animals it is only $\frac{1}{4}$. Radical operation in both half-grown and full-grown animals causes an initial but transitory increase in the siderophil granules of the adrenal cortex. Essentially the same changes as in total castration follows displacement of the testes into the abdominal cavity and since in these cryptorchid testes the germinal epithelium is atrophic while the Sertoli cells and interstitial cells remain normal or hypertrophied, the conclusion is drawn that it is cessation of spermatogenesis that is related to the adrenal changes. Ovarian transplants in animals with normal spermatogenesis accelerate pigment formation in the cortex of the suprarenals. In animals where ovarian transplants have enlarged the nipples, there is generally a direct correlation between the size of the nipple on one hand and the size of the follicles and hypertrophy of the granulosa cells on the other. The general conclusion is that the structure of the supra-

renal cortex, like secondary sex characters generally, are dependent to a considerable extent upon the condition of the gonads.—A. T. R.

An experimental study of the adrenal cortex. II. Prolongation of life after complete epinephrectomy. Zwemer (R. L.), *Am. J. Physiol.* (Balt.), 1927, **79**, 658-665.

Feeding of thyroid substance to four normal cats caused a decrease in the weight of the animals. This is believed by the author to be due to the dehydrating effect of the thyroid, and to the increased metabolism. The removal of the thyroid glands in 11 cats prolonged the life of animals deprived of their adrenals to an average of 200 hours. The absence of the thyroid apparently tends to decrease the elimination of water, and the symptoms of adrenal insufficiency, which strikingly resemble those of anhydremia, are postponed. An excess of thyroid substance, produced by daily feeding of the desiccated gland, during the interval between the removal of the first and second adrenal, hastened the death of six epinephrectomized animals. The thyroid appears to increase the elimination of water from the organism, thus adding to the dehydration effect following adrenal extirpation. The animals survive on an average only 18 hours after the removal of the second adrenal. The oral administration of a 5% solution of glucose, if given in sufficient quantities, will prolong the life of epinephrectomized cats for an average of 220 hours (7 cases reported).—R. G. H.

Relation of facial hirsutism in women to the gonads, suprarenals and hypophysis (Zur Frage der Gesichtsbehaarung bei Frauen in Zusammenhang mit Keimdrüsen, Nebennieren und Hypophyse). Berblinger (W.), *Ztschr. f. Konstit.* (Berl.), 1926, **12**, 193.

A discussion of the evidence for associating the excessive growth of hair on the face in women with disfunction of gonads, suprarenals and hypophysis. Several cases are given of facial hirsutism in women and abnormalities in hair development in men as correlated with the size and condition of the above glands. The author considers it questionable if the presence of a beard in women is related to hypophyseal disorders.—A. T. R.

Dermatosis and glands of internal secretion (Dermatosis y glándulas de secreción interna). Bonilla (E.), *La Medicina Ibero* (Madrid), 1925, **395**, 556-563; **Recurrent erysipelas and thyroid-ovarian insufficiency** (Erisipelas de repetición e insuficiencia tiro-ovarica). Bonilla (E.), *Arch. d Med. Cirugia y Especialidades* (Madrid), 1926, **10**, 457-463.

The author maintains the existence of an indubitable relation between the endocrine and vegetative nervous structures and der-

matosis. He believes that disfunction of the former give rise to metabolic disturbances which condition the latter. The unquestionably favorable therapeutic results following gland administration in certain skin disorders (eczema, psoriasis, etc.) are thus to be explained as secondary reactions to the correction of metabolic deficiencies. In a case of recurrent erysipelas, thyroid-ovarian treatment was remarkably successful.—G. M.

Observations bearing upon the interrelation of insulin and other gland extracts in metabolism. Cammidge (P. J.) & Howard (H. A. H.), *J. Metabolic Research* (Morristown), 1924, 6, 189-194.

Respiratory quotients were determined in 12 rats, starved 24 hours; in 6 rats and 9 guinea pigs after feeding; 12 rats after insulin, before and after feeding; in 6 rats and 6 guinea pigs after adrenalin subcutaneously administered, and various animals after thyroid and parathyroid injections. Summarizing tables are included. It was concluded that, taken as a whole, the results of these observations show that under the influence of insulin the tissues in a fasting animal utilize more carbohydrate in place of the protein and fat upon which they were depending, but that when insulin is administered to a previously fed animal there is only an alteration in the rate and not in the nature of the metabolism. Although adrenalin, like insulin, increases the respiratory quotient in the fasting state, the effects of the two on metabolism are antagonistic, the simultaneous injection of suitable doses producing the same metabolic changes as in a normal animal. The influence of insulin upon metabolism is also neutralized by pituitrin, but as pituitrin alone does not affect the respiratory quotient or oxygen consumption, the means by which this result is brought about is obviously different and probably depends upon a direct chemical interaction between the two hormones and not upon an opposition in their functions in metabolism as is the case with insulin and adrenalin. Thyroid and insulin have apparently no direct influence upon each other, nor are the effects of the one upon metabolism influenced by the other, but the action of insulin upon the utilization of carbohydrate is very materially increased by parathyroid. In fed animals the injection of adrenalin, pituitrin, or thyroid was found to give rise to the appearance of more or less sugar in the urine; the glycosuria was prevented, however, in all instances when insulin was administered at the same time.—R. G. H.

Treatment of infantilism (*Zur Therapie des Infantilismus dystrophicus universalis*). Chetivismus (S.), Schweiz. Med. Wchnschr. (Basel), 1926, 56, 756-776.

The concept of infantilism as being essentially a state of hypogonadism is too narrow. In infantilism the whole organism is underdeveloped, the hypogonadism being merely a constituent of

the symptomatology. Indeed, it is not hypogonadism but merely a retardation of gonadal development (metagenatilisim) that is observed in infantilism. Hence Lorain's definition of infantilism must be broadened to include an underdevelopment of body and mind. The clinical picture varies with the time of appearance of the disease; whether it develops in early childhood, or before puberty, or afterwards. If it develops during early childhood, the patient is small, emaciated, with infantile physical and mental habitus. The head is somewhat large, but the body is proportionately built. The lymphatic system, including the thymus, may be prominent. If the disease develops at puberty or shortly after, the retardation of growth is less evident, and hypogonadism is the most prominent feature. Here a differential diagnosis, from eunuchoidism is difficult to make. If the disease does not appear until after the time of puberty, there is no evident retardation of growth, and the gonads are relatively well developed. The growth of beard and hair elsewhere is sparse, and there is defective or retarded mental development. The term juvenilism is aptly applied to these subjects. In view of pathological changes discovered in various endocrine organs in these subjects, the cause of infantilism is essentially a pluriglandular insufficiency, which in turn probably depends upon toxic influences. Treatment with ovarian, pituitary, thymus, and suprarenal substances are discouraging, despite good reports from other authors. Thyroid medication was found to be very useful in two cases detailed in this paper. Treatment should be carried out for at least three months before deductions as to its efficacy are drawn.—I. B.

Otosclerosis. Drury (D.), *Ann. Otol., Rhin. & Laryn.* (St. Louis), 1926, **35**, 651-681.

The author reviews the literature on the possible relation of various endocrine glands to otosclerosis and discusses some of his own data obtained in a study of more than 100 cases. Two illustrative cases are reported. He concludes that it would seem to be established that many and widely divergent factors can excite the appearance of otosclerosis in a predisposed person. The essential factor underlying the morbid change is possibly a chemical one affecting the nutritive stability of developing and fully developed bone and cartilage. In a dominant percentage of cases the several endocrine glands are direct etiologic factors through their influence on normal metabolism. In cases of otosclerosis without firm ankylosis of the footplate of the stapes or other irreversible organic changes, a response to the proper glandular treatment may be expected with reasonable confidence. The constitutional tendency or hereditary influence would seem to be a dominant factor in determining the condition of otosclerosis where an endocrine or nonendocrine pathol-

ogy produces disturbances of metabolism. The work so far done is to be regarded as suggestive rather than definitive of a possible ultimate solution of the highly complex problem of the etiology of otosclerosis.—R. G. H.

Anatomical alterations in experimental cocaine poisoning, with particular regard to the endocrine glands (*Ricerche su le alterazioni anatomiche nell' avvelenamento sperimentale da cocaina, con particolare riguardo alle glandole a secrezione interna*). Falco (G.), Arch. di farmacol. sper. (Roma), 1925, 40, 164-219

This is a rather complete study of the action on the different organs of toxic doses of cocaine. The drug was administered subcutaneously, by nose, pharynx and stomach. The author noted marked alterations of the nervous system, liver, kidney and heart. Nearly all the endocrine glands showed some alteration. The testis was especially studied. One testis was removed for control. The subjects were 4 dogs, 4 guinea pigs and 2 rabbits. In the surviving testis are separately considered the modifications from hemi-castration as well as the cocaine. The organs were diminished in volume with reduction of the spermatogenesis and increase of interstitial tissue. If the testis is less functioning, then the interstitial reaction is more evident. There is also edema of the interstitial tissue. Testis lesions are like those from alcoholic intoxication. The author holds that the testicular effect is secondary to that on the nervous system.—P. M. N.

Observations on the influence of a glycerine emulsion of testes and adrenals on tuberculosis and senile patients. Korenchevsky (V.), Lancet, (Lond.), 1925, 209, 1056-1060.

Observations made on 70 tuberculous patients and 14 seniles indicate no essential efficiency in the method of oral administration of preparations of testes and adrenals. In the observations made on senile patients the only noteworthy effect was that the ingestion of glycerine emulsion of testes and adrenals had produced a slight improvement in their intelligence and memory and in some patients in their muscular strength.—Author's Abstract.

The influence of the removal of the thyroid, parathyroid and sexual glands and of thyroid feeding upon the regulation of the body temperature of rabbits. Korenchevsky (V.), J. Path. & Bacteriol. (Lond.), 1926, 29, 461-472.

One hundred and four experiments were performed on 28 rabbits, 19 on normal, 15 on thyroidectomized, 11 on castrated and 19 on parathyroidectomized rabbits and 40 on rabbits in which two or three of these glands had been removed. In the "warming"

experiments the rabbit was placed in its cage in the hot room which was at a temperature of 37.50°C . In the "cooling" experiments the rabbit was placed in a jar of water at 14.5°C . for 4 minutes. The wet rabbit was then kept in the room. The cooling of normal young rabbits produces a more pronounced fall of the body temperature than the cooling of normal adult rabbits. After thyroidectomy, cooling the rabbits causes a much more pronounced fall, and warming a much less increase of the body temperature than is observed in the normal animals before removal of the thyroid glands. Some adult thyroidectomized rabbits may even die after a degree of cooling which normal rabbits are always able to resist. The cooling of young thyroidectomized rabbits is lethal under those conditions which in the same rabbits before the operation produced only a temporary fall of body temperature. Parathyroidectomy does not change in a marked degree the above mentioned response of normal or thyroidectomized rabbits to cooling or warming. The influence of castration on the response of rabbits to cooling or warming seemed to be similar to that of thyroidectomy, but the changes produced were much less marked. The cooling of two rabbits in which both sexual and thyroid glands had been removed was followed by a lethal fall of the body temperature. Rabbits in which the thyroid, parathyroid and sexual glands had been simultaneously removed responded to cooling or warming in the same way as thyroidectomized animals. The response of thyroidectomized rabbits to cooling or warming may be restored to a normal degree by thyroid feeding. After long and excessive thyroid feeding warming the rabbits may even be followed by a lethal overheating of the animal with a rise of the body temperature of 43.5°C . The author concludes that the thyroid gland plays an important part in the regulation of the body temperature, and therefore its condition has always to be taken into account in considering the resistance of different individuals to cold or heat, and also in the diseases accompanied by fever. The above results are in agreement with previous experiments of the author and his co-workers, published in detail in Russian, in which it was shown that the nitrogenous and gaseous metabolism of dogs and rabbits decreases after the removal of the thyroid glands. Tables showing these results are published in the present paper.—Author's Abstract.

Combined skull necrosis, exophthalmos, Fröhlich syndrome and diabetes insipidus [Breitrag zu einem seltenen Symptomenkomplex. (Schädelerweichungen, Exophthalmus, Dystrophia adiposo-genitalis, Diabetes Insipidus)]. Kyrklund (K.), Ztschr. f. Kinderh. (Berl.), 1926, 41, 56.

The author reports a very rare and remarkable symptom-complex in a child 12 years of age, who was normal at birth and walked

and talked at the normal age. The illness began at 4 years of age and was characterized by extreme thirst and polyuria (diabetes insipidus). At 7 years, the child suddenly began to get fat. This adiposity continued and was accompanied by exophthalmos and headaches. Later she walked stiffly and complained of achy limbs. The scalp became so tender that the hair was cut. Menstruation had not appeared. Skeletal growth and mental development were retarded from the onset of the illness. The examination showed a short, weak child with the Fröhlich type of obesity. The fat was tender (adiposis dolorosa). There was some cyanosis of the lips, hands and feet; otherwise the skin was normal. There was no pubic hair. The nose was somewhat broad as to base. There were several peculiar, painful irregularities in the parietal bones (soft in their centers, 3 to 4 cm. in diameter); these areas appeared as irregular defects in roentgenograms. The sella turcica appeared to be normal; the teeth were carious. The child weighed 28 kilograms and her height was 113 cm. There was marked exophthalmos. The urine test was negative; the output was 3000 cc. in 24 hours. The Pirquet test was plus—the Wassermann was negative. The child was given anterior pituitary tablets (Parke, Davis & Company) and improved. After two weeks the medication was interrupted and the patient became worse. Two weeks later the pituitary extract was resumed, but a week later the patient died suddenly. The autopsy disclosed no mammary tissue. The softened areas in the skull extruded a yellowish detritus, and were of crater-like formation. The sella turcica was normal. The dura was lightly adherent to the inner table of the skull in the defective areas noted above. The thymus, heart, liver, spleen, kidneys and suprarenals were normal. The uterus and ovaries were small. No microscopic alterations were found in any of the ductless glands. However, tumors resembling spindle cell sarcomata were found in the brain stem behind the hypophysis in the skull, and in one kidney. Staining for tubercle bacilli proved negative.

The author refers to six other cases in the literature, being unaware of another remarkable instance reported recently by Dunn of Omaha. He believes the primary cause in his own case to be multiple sarcoma-like tumors. The dwarfism, dystrophia adiposogenitalis and diabetes insipidus he refers to an incretory disturbance of the hypophysis, secondary to the blocking of the secretory pathway from a normal hypophysis, by the tumor in the brain stem. He believes the etiological agent responsible for the membranous bones to vary in different cases, being malignant in some and infectious in others. This symptom-complex has been called Christian's syndrome.—H. L.

The relation between the thyroid and the cholesterine and phosphate change in the blood, the adrenals, and the sexual glands (*Sui rapporti tra la tiroide ed il ricambio colesterinico e fosfatidico del sangue, del la capsule surrenali e delle glandole sessuali*). Pighini (G.) & De Paoli (M.), *Biochim. e terap. sper.* (Milano), 1925, 12, 49-71.

Following administration of thyroid material to animals there were seen modifications in cholesterine-lipoid content in the organs most related to that exchange; modifications in the relation between cholesterine and phosphorated lipoids (phosphatides); alterations of these organs by the long administration of the thyroidine. Histological and chemical examinations were made of the blood, the adrenals and the sexual glands. Experiments were conducted on twenty guinea pigs, ten males of the same weight and ten females in various periods of pregnancy, and also on three men in good health (*naturally in the three men, only blood examination was possible*). The authors conclude that the cholesterine and lipoids probably serve to fix and neutralize the thyroid hormone in hyperthyroidism; these increase in the blood while diminishing in the adrenal cortex, which is stimulated to a greater functional rhythm, analogous to that of the sexual glands. The adrenals in hyperfunction increase in mass and in the adrenalin production, which is correlated with the preceding fact. The sexual glands arrest the elaboration of the lipoid products that function in the metabolic processes of the germinal elements. Phosphatide modifications are in relation with those of the cholesterine.—P. M. N.

The incretory processes of the ovary and of the adrenal cortex (*Die inkretorischen Prozesse des Drüsenparenchyms des Ovariums und der Nebennierenrinde bei vitaler Färbung*). Sserdjukoff (M.), *Arch. f. d. ges. Physiol. (Berl.)*, 1926, 214, 196-206.

The parenchymatous elements of the cortical substance of the adrenals and of the glandular portions of the ovaries exhibit in different degrees power of storage of vital stains. The unequal coloration of the protoplasm of epithelial elements of adrenal cortex, epithelial cells, corpus luteum, and interstitial cells of the ovary correspond to the different secretory cycles of their protoplasm and to the degree of intensity of the incretory processes within them. Storage depends partly on the affinity of the protoplasm for the colloidal solutions.—A. T. C.

Roentgenotherapy in psychiatric and neurological diseases in childhood (*Roentgentherapie bei psychiatrischen und neurologischen Erkrankungen in Kindesalter*). Weiser (W.), in Press, *Ztsch. f. Kinderfors* (Berl.).

Based upon radiations in 300 cases during the past three years.

Diagnosis was made by aid of Abderhalden ferment reaction, gas metabolism and clinical findings. The glands radiated were the hypophysis, thyroid and genitals and also the base of the skull with doses ranging from 2 to 10% H.E.D. The average time of treatment until the appearance of improvement was three months, but in one protracted case it was twelve months. Treatment was given at intervals of four weeks and after signs of improvement were noted, six to twelve weeks. One or more series were given depending upon each individual case. It was noted in some cases that after the first treatment there was a retrogression, which, however, proved amenable to treatment with further radiation. In encephalitic conditions, as in disturbances of the hypophysis or in raying the base of the skull, it is best not to start with more than 2% H.E.D. Other general treatment such as organotherapy, anti-syphilitic remedies, etc., may be administered during the course of the series. Very marked improvement is reported in cases of idiocy, imbecility, pituitary disturbances, mongolian idiocy, Little's disease, behavior psychosis, post-encephalitic disorders, dysgenitalism, and chondrodystrophy.—M. B. G.

Experimental researches on the sexual hormones (Ricerche sperimentali sulla iperormonizzazione sessuale). Bertolani De Rio (Maria), Arch. di Sc. biol. (Napoli), 1925, 7, 402-420.

To pairs of rabbits were administered homologous sexual gland grafts and injections of extracts of the same glands. The generative aptitudes are conserved at least until the second generation, and for some seem almost exalted. The sexual glands histologically studied showed evidence of hyperfunctioning: in the testis was seen reduction of interstitial tissue; in the ovary this was increased secondarily to augmented follicular atresia. In the sons was noted some limitation in the activity of cartilage increase.—P. M. N.

The syndrome of Block (El síndrome de Block). Bonilla (E.), Arch. d. Endocrinol. y Nutrición (Madrid), 1926, 5, 305-325.

In 1916 Block described a syndrome which was presented by a woman who was unable to satisfy her sexual desire. This was characterized by nervous and psychic agitation, menstrual disturbance and a pigment which localized principally in the cheeks and in the forehead, and sometimes in the thighs. Block believed that the condition amounted to a sexual disorder, leading secondarily to alterations of the endocrine glands, especially the suprarenals. Bonilla has studied eight cases and come to the following conclusions: The syndrome of Block is an indubitable clinical entity; the fundamental endocrine condition is ovarian insufficiency fol-

lowed sometimes by secondary hyperthyroid reaction; the melanoderma of Block's syndrome is not due to insufficiency of the suprarenal glands, but to ovarian insufficiency.—G. M.

Cyclic changes in Bidder's organ, and gonads of the toad [Die Geschlechtsmerkmale im Lebenszyklus der männlichen und weiblichen Kröten (*Bufo vulgaris* Laur)]. Eggert (B.), Ztschr. f. Anat. u. Entwicklungsgesch (Berl.), 1926, **79**, 457-497.

Bidder's organ produces a fatty incretion beginning in May, at the close of hibernation, and continuing till June, when regeneration sets in. By August the organ has been fully restored again. The well known cyclic changes in the ovary and testis are recounted. The glands in Muller's duct also show periodic changes by discharging mucous during rut.—A. T. R.

Eunuchoidismus mulierum verus connatus. Galant (J. S.), Ztschr. f. Konstit. (Berl.), 1925, **12**, 70-76.

The physical measurements of a 19-year-old woman, 154 cm. in height and weighing 48 kgm. is given. The diagnosis is based principally on the condition of the genitals. Pelvis is of the masculine type. There are no mammary glands. The labia majora and clitoris are underdeveloped. The labia minora are lacking. The vagina is narrow and short, and the uterus is about the size of a thimble. The ovaries and tubes are not palpable. Libido, however, is strong.—A. T. R.

Neural progressive muscular atrophy and disorders of inner secretions (Neurale progressive Muskelatrophie und Störungen der inner Sekretion). Herzog (I.), Med. Klin. (Berl.), 1926, **22**, 1300-1301.

Herzog reports one case of neural progressive muscular atrophy, describes an untreated twin brother, and states that two relatives of these boys have been in a local hospital suffering from ambulatory trouble. The case reported was that of a tall man with elongated extremities with general musculature weak and overlaid with fat. He had a feminine appearance but with developed hair, including beard. The genitalia were well developed. The electrical excitability of nerves diminished. No response could be elicited from the atrophic muscles. Treated with testicular extract the patient reported improvement within one-half hour. Later his hands were noticeably improved and he was able to take two-hour walks. When medication was left off weakening was felt. After eight years the condition is approximately as after the first. The electrical excitability of the nerves remains uninfluenced.

—R. M. Oslund.

The effect of light upon the follicular hormone. Jordan (C. N.) and Doisy (E. A.), *Proc. Soc. Exper. Biol. & Med. (N. Y.)*, 1926, **24**, 216-218.

Diffuse sunlight very rapidly destroys the physiological activity of the purified hormone.—J. C. D.

Structure of the embryonal ovary of the horse with special reference to the interstitial cells (Über den Bau des embryonalen Pferdeierstockes. Ein Beitrag zur Kenntnis der Zwischenzellen). Kohn (A.), *Ztschr. f. Anat. u. Entwicklungsgesch. (Berl.)*, 1926, **79**, 366-390.

The enormous masses of epitheloid cells which are found in the medulla of the embryonal ovary of the horse and which are present long before follicular formation begins, arise from the germinal epithelium. These cells have the general characteristics of interstitial cells, but their relation to the so-called interstitial cells of the adult ovary is not clear.—A. T. R.

The sexual glands and metabolism. IV. The influence of injections of emulsions of testes and prostate and of insulin-like testicular extracts upon the nitrogen metabolism of normal, castrated and

thyroidectomized rabbits. Korenchevsky (V.), *Bio-Chem. J. (Liverpool)*, 1925, **14**, 773-782.

Twenty-three experiments were performed on 12 rabbits, of which 4 were castrated, 4 thyroidectomized, 3 both thyroidectomized and castrated, and 1 normal. An homologous emulsion of testis decreased the nitrogen metabolism of thyroidectomized rabbits much more than that of normal or castrated animals. This emulsion also decreased urinary flow to about the same degree in rabbits both with and without thyroid glands. The insulin-like substances isolated from testis substance and injected into thyroidectomized animals also produced a more pronounced decrease in nitrogen metabolism than in rabbits with thyroids. These substances decreased the excretion of urine in both thyroidectomized and non-thyroidectomized animals during the periods following the period of injection, as did testicular emulsion. During the period of injection itself the flow of urine increased in about one-third of the experiments and decreased in the other two-thirds. Thyroid hormones appear to counterbalance the depressing influence on the metabolism of rabbits produced by an emulsion of rabbit's testis or of testicular insulin-like substances. The similarity between the effects of testicular emulsion and of the insulin-like substances extracted from testis suggests that in the former case the fall in nitrogen metabolism, and possibly in urinary flow, is in part due to the presence of insulin-like substances in testes. The same explanation

might apply to the decrease in the nitrogen metabolism of rabbits after an injection of kidney emulsion since insulin-like substances have also been isolated from the kidney. An homologous emulsion of prostate alone produced practically no change in the nitrogen metabolism of thyroidectomized rabbits, whereas in that of rabbits with thyroid glands a definite increase was observed. Prostate emulsion appears to increase nitrogen metabolism of rabbits by stimulating the activity of the thyroid gland. Prostate emulsion increased the flow of urine in the thyroidectomized rabbits, whereas, on an average, the excretion of urine was decreased in rabbits with thyroid glands.—Author's Abstract.

The sexual glands and metabolism. III. The influence of injections of testicular or ovarian emulsions upon the nitrogen and gaseous metabolism of dogs and rabbits. Korenchevsky (V.), Brit. J. Exper. Pathology (Lond.), 1925, 6, 158-171.

Experiments were performed on 35 dogs (11 males and 24 females) and 8 female rabbits, some experiments being repeated twice or three times on the same animal. The emulsions were freshly prepared with saline solution from the sexual glands of dogs or cows. As in the case of castration the injection of an emulsion of testis has not always the same uniform effect upon the metabolism of animals and human beings. This divergence occurs not only among different species of animals, but even among the different individuals of the same species. However, the injections of testis emulsion produced the same effect on most animals of the same species. Neither ingestion nor injection of testicular preparations altered the gaseous metabolism of rabbits definitely. When a homologous emulsion of testis was injected into rabbits their nitrogen metabolism was slightly decreased, but only to the same degree as was observed after the injection of emulsions of other tissues, as for example, the kidney. The injections of a homologous testicular emulsion into dogs produced a rise in the nitrogen metabolism of nearly all castrated and both castrated and thyroidectomized animals. This effect was seen in only 1 of the 3 normal dogs. In the control period immediately following the period of injections the nitrogen metabolism of most dogs dropped considerably below normal. These injections only changed the gaseous metabolism of dogs a little, if at all, in which case it was usually decreased. Subcutaneous injections of an emulsion or extract of the whole ovaries in most cases produced an increase in the nitrogen metabolism. Those of an emulsion or extract of corpora lutea in most cases decreased the nitrogen metabolism. Those of an emulsion or extract of the remaining ovarian tissue increased the nitrogen metabolism. The effects of these different ovarian tissues usually were most pronounced during the first four hours after the injections. In most

experiments neither of these preparations from the ovary had any constant or definite effect upon gaseous metabolism. A decrease in the nitrogen metabolism after injection of the whole ovaries can be caused partly by the principles of the corpora lutea prevailing, whereas an increase may be produced by the remaining ovarian tissues being dominant. In the pregnant animal influence of her own corpora lutea upon metabolism seemed to increase the effect of the injections of the emulsion of these glands. The lowered nitrogen metabolism observed during "heat" in animals, menstruation in women, and pregnancy in animals and women is probably to some extent controlled by the internal secretions from the corpora lutea. The varying effects upon the nitrogen metabolism obtained after injections of emulsions of testis or ovaries may possibly be explained by the presence in them of specific (e.g., corpora lutea in ovaries) or of non-specific (e.g., insulin-like substances) principles; by the varying degree of functional efficiency and therefore the varying reaction of the endocrine glands, which are influenced by the injections and in non-castrated female animals by the different stages of development of the corpora lutea or of the remaining ovarian tissues in their own ovaries.—Author's abstract.

Female sexual hormones (Thelykinins). XIII. Thelykinin action in birds. [Ueber weibliche Sexualhormone (Thelykinine)]. XIII. Beobachtungen zur Frage der Thelykininwirkung an Vögeln.) Loewe (S.), Voss (H. E.), & Paas (Elisabeth), *Arch. f. d. ges. Physiol.* (Berl.), 1927, **215**, 453-456.

Injection of ovarian extract into two old hens was followed by short period of active egg-laying.—A. T. C.

Three cases of pseudohermaphroditism (Sobre tres casos de pseudohermafroditismo). Lopez (V.) & Lucas (S.), *Arch. d. med. Cirugia y Especialidades* (Madrid), 1926, 529-536.

The authors have studied histologically the testicles in three cases of pseudohermaphroditic gynandroids. The most interesting finding was the abundance of interstitial cells which formed islands of cells of various sizes and irregular contours. The germinative cells were completely atrophied. In one of the cases large masses of Sertoli tissue were found. The anomalous development of the interstitial glands in these cases has obscured their physiological significance and explains the disparity of the criteria in determining the sex characters. Some authors, as Ancel and Bouin, Steinach and others, maintain that the interstitial cells serve as the determining character, while others, as Voronoff, believe that the characteristics are dependent exclusively upon the germinative cells, which form directly a special internal secretion, as a result of the resorption of sperma.—E. B.

Cryptorchid testes and testicular hormone production. Oslund (R. M.), *Am. J. Physiol. (Balt.)*, 1926, **77**, 76-82.

An extensive study of the condition of the germinal epithelium in cryptorchid testes of man, dog, sheep and pig. Only abdominal testes were studied with special attention to regenerative or spermatogenic possibilities and the source of the testicular hormone which continues to be present. It was found that Sertoli cells are found along the basement membrane of the tubules. Their structure is quite different from Sertoli cells of normal testes. Other cells found in the lumen of these tubules are products of the so-called Sertoli cells. The latter are indifferent cells of the germinal epithelial line. From these indifferent cells develop Sertoli cells and spermatogonia of normal testes. In testes recovering from exposure to x-rays these modifications have been seen by the author. Germinal epithelium is therefore present in cryptorchid testes and the testes possess regenerative possibilities. Obviously there is a good possibility that the germinal epithelium takes part in the production of the testicular hormone. At least it cannot be said that there is no germinal epithelium and therefore that the interstitial cells only could produce the hormone.—Author's Abstract.

Ligation of vasa efferentia in rats. Oslund (R. M.), *Am. J. Physiol. (Balt.)*, 1926, **77**, 83-90.

Twenty-five experiments on albino rats were performed in which the vasa efferentia were ligated without injuring the vascular system. The animals were killed from one day to two months later. Ligation of the vasa efferentia produces an accumulation of spermatogenic cells and of colloidal material in the seminiferous tubules. This causes enlargement of the tubules, and distention of the testis. Degeneration of germinal epithelium follows with decrease in testicular and seminiferous tubule volume. The necrotic material is absorbed from the testis. The degeneration progressed throughout the two months of observation and there was no sign of recovery. No interstitial cell hypertrophy was found.—Author's Abstract.

Studies on the internal secretion of the ovary. I. The distribution in the ovary of the oestrus-producing hormone. Parker (A. S.) & Bellerby (C. W.), *J. Physiol. (Lond.)*, 1926, **61**, 562-575.

A detailed description of experiments on the preparation and testing of extracts from whole ovaries without corpora lutea, from liquor folliculi, young and mature solid corpora lutea, hollow corpora lutea and residual tissue, in order to determine the distribution of the hormone in the organ. The yield per kgm. varied between 0.9 gm. for liquor folliculi and 4.76 gm. for the residual

tissue. For the entire series of experiments the activity of residual tissue was 50% higher than for the liquor folliculi in total yield. But computed in mouse units the activity of the liquor folliculi was two and one-half times as great as for residual tissue. In view of previously reported evidence that ovaries consisting entirely of extra-follicular tissue can produce normal oestrous cycles, the authors propose the term "oestrin" to designate the hormone instead of "folliculin."—C. I. R.

Quantitative studies on the effects of inanition, overfeeding and feeding thyroid gland on the testis (Untersuchungen über die männliche Keimdrüse der weissen Hausmaus. Ein Beitrag zur Frage der Wechselbeziehungen zwischen Keimdrüse und Gesamtkörper und der Bedeutung der Keimdrüsenzweischenzellen. I. Teil: Einleitung, allgemeine Versuchsanordnung und Mengenbestimmungen). Saller (K.), *Ztschr. f. Anat. u. Entwcklgs-gesch.* (Berl.), 1926, 80, 579-668.

Careful quantitative methods applied to the testes of white mice after acute inanition showed a decrease in the interstitial cells. The ratio of interstitial tissue to the tubules may become as small as 1:26 as compared with normal ratio of 1:10. In chronic inanition the loss in interstitial tissue is less, the above ratio being 1:13 or 1:14. In overfeeding the results were more variable. While the interstitial cells, as well as the germinal tissue, may be damaged and reduced in some individuals, others showed practically no change or a slight increase. Occasionally the proportion of interstitial tissue to the tubules becomes 1:6 as compared with the normal ratio of 1:10. Feeding large doses of thyroid gland ultimately causes testicular atrophy—the interstitial tissue suffering most. Small doses may also damage the germinal epithelium with hypertrophy of the interstitial tissue, relatively and probably also absolutely.—A. T. R.

Symptoms associated with the menstrual cycle and the effects thereon of ovarian therapy. Sharlit (H.), Corscaden (J. A.) & Lyle (W. G.), *Am. J. Obst. & Gyn.* (St. Louis), 1925, 10, 246-253.

The authors administered desiccated ovarian substance (Lehn and Fink) to 132 women showing classical climacteric symptoms, and especially "flashes." They considered their results in the light of the following criteria: effective therapy should be followed by a percentage of cures that indisputably establish the value of the therapeutic agent. The interval between the beginning of the treatment and the appearance of relief should be reasonably comparable in all cases, even in those showing considerable differences in the duration of the disorder. Furthermore, there should be evidenced a distinct relationship between dosage and effect; and a

subtherapeutic dose ought readily to be demonstrated. Demonstrations and occurrences such as these permit of a reasonable certainty that relief after therapy is not simply coincidental. On this basis it is concluded that the therapeutic results were unquestionably favorable.—R. G. H.

On the interruption of pregnancy in the rat by the injection of ovarian follicular extract. Smith (Margaret G.), Johns Hopkins Hosp. Bull. (Balt.), 1926, 39, 203-214.

Water emulsions of residue from lipid extracts of ovarian follicular contents injected during the first five days after mating interrupted pregnancy. On the first day three or more rat units were required to produce this result and as pregnancy advanced an increasing concentration of 10, 20 and 40 rat units were required. These experiments were carefully controlled and the results clear-cut.—E. Allen.

Genital system responses to daily, pituitary transplants. Smith (P. E.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1927, 24, 337-338.

Such homeo-transplants made into young male rats produce first enlargement of the genital system exclusive of the testes. After prolonged treatment the testes also show a striking enlargement over those of the controls. After castration the transplants have no effect. Guinea pig pituitary used on rats is ineffective.—J. C. D.

Ovarian heterografts in various endocrinopathies (Hetero-transplantations de l'ovaire dans diverses endocrinopathies). Serdjukoff (M. G.), Rev. Française d'Endocrinol. (Par.), 1926, 4, 321-331.

Serdjukoff made transplantations of goats' ovaries into fifteen women, most of whom were suffering from hypo- or dys-ovarian function. Their principal complaints were insufficient menses, vertigo, progressive obesity, headaches, hot flushes, lessened sexual impulses, weakness and depressed state. The average age of the women was between 28 and 39 years. In ten there was an evident disproportion between weight and girth measurements with marked general obesity. In most of the cases there was an increased tone of the sympathetic nervous system. The ovaries were small or showed cystic degeneration in all cases. Preliminary organotherapy from six months to a year by injections of ovary, thyroid and pituitary and similar combinations gave no result. The ovaries taken from the goats were cut in two, warmed in physiological salt solution, and placed between the separated fibres of the rectus muscle. There was a swelling and sensitiveness in the region of the transplants on the fifth day in five cases. Immediate results were: re-appearance of menses in 10 days after a six-month absence; intensification of regular menses; return of sex impulse in 10 to 14 days;

general state of euphoria, and loss of weight of 3, 5, 8 kilograms. The cases were observed from two months to one year. It was noticed that general vivacity and vigor replaced mental depression. Serdjukoff considers ovary transplantation a means of diagnosis in ovarian dysfunction for in cases of mixed endocrinopathies the operation had no effect upon the patient. In true diseases of the ovary, noticeable effects were produced by the transplantation.

—L. L. Stanley.

A hormone of heart movement. V. Further experiments with extracts of frog's heart (Ueber ein Hormon der Herzbewegung. V. Weitere Versuch mit Froschherzextrakten). Haberlandt (L.), Arch. f. d. ges. Physiol. (Berl.), 1926, **214**, 471-481.

The active substance is present in alcoholic extracts, decomposing very slowly (active after 25 days), is insoluble in ether, and cannot therefore be of lipoid nature, and is very difficultly soluble in chloroform. It is dialysable and heat-resistant. It is not of adrenine nature, since test on the Lăwen-Trendelenburg preparation shows no definite constriction of the vessels, and may produce a relaxation.—A. T. C.

Anthropometric analysis of growth disturbances in hypophyseal diseases (Versuch einer anthropometrischen Analyse der Wachstumsstörungen bei hypophysären Erkrankungen). Ballmann (E.) & Hock (J.), Ztschr. f. Konstit. (Berl.), 1926, **12**, 540-553.

Tables and schemas showing the physical measurements of five boys from 13 to 19 years of age and two adults (42 and 62 years of age). Three of the boys are dwarfed and two excessively fat (dystrophia adiposogenitalis). One of the adults apparently has a hypophyseal tumor of long standing. The other one is classed as a eunuchoid.—A. T. R.

Acromegaly. Bernstein (M.), Boston M. & S. J., 1926, **195**, 1244-1245.

Report of a patient whose headaches were relieved and eyesight preserved for eight years, as a result of hypophyseal operation.—J. C. D.

Hypophyseal obesity of syphilitic origin (Hipofisaria de origen sifilitico). Bonilla (E.), La Medicina Iberia (Madrid), 1926, **449**, 689-693.

Some authors insist on the syphilitic etiology of endocrine diseases, saying that the hypophysis is affected by this infection. The author has observed two cases of hypophyseal obesity of syphilitic origin, confirmed by radiography of the sella turcica. In the two

cases the basal metabolic rate was low, as previously shown by the observations of Marañón and Labbi, Stevenin and Van Bogaert; one of the cases was of special interest because with antisyphilitic treatment the weight dropped from 110.500 to 90 kgm. in three months and the basal metabolic rate was raised. These are the first observations in the literature which show the influence of antisyphilitic treatment upon basal metabolism.—G. M.

The pituitrin sensitivity of the human organism. Csepai (K.) & Weiss (I.), *Ztschr. z. d. ges. exper. med.* (Berl.), 1926, 50, 745-753; *Abst., Chem. Absts.*, 20, 269.

The intravenous injection of a small quantity of pituitrin leads to a rise in blood pressure from 15 to 25 cm. and lasting about two minutes. In many pathological conditions the pituitrin sensitivity remains normal, but it is heightened in Basedow's disease and hyperthyroidism and lowered in dystrophia adiposogenitalis and hypothyroid infantilism.

Hypophysectomy and replacement therapy. Foster (G. L.) & Smith (P. E.), *J. Am. M. Ass.* (Chicago), 1926, 87, 2151-2153.

The basal metabolism of totally hypophysectomized rats was found to be about 35% below the average of a series of normal animals. The metabolic rate of these animals was restored to normal by daily anterior pituitary homotransplants or by daily injections of thyroid extract, but not by daily injections of posterior lobe extract. The specific dynamic action of glyocoll proved to be absent in hypophysectomized animals and apparently can be restored only by replacement of both anterior and posterior lobe, but not by either one alone.—R. G. H.

The influence of pituitrin administration upon certain phases of carbohydrate metabolism. Hines (H. M.) & Leese (C. E.), *Proc. Soc. Exper. Biol. & Med.* (N. Y.), 1926, 24, 213-215.

Dogs were injected intravenously with glucose alone and also with glucose combined with commercial pituitrin. In the latter experiments there was increased glucose excretion. There was no increased concentration of the glucose in the urine, no change in the pH or carbon dioxid content in the blood, and no change indicated in the quantity or quality of the oxidative processes. The pituitrin acts, therefore, by decreasing the rate at which the tissues remove the glucose from the blood.—J. C. D.

The action of pituitary upon the pregnant uterus of the rabbit. Knaus (H. H.), *J. Physiol.* (Lond.), 1926, 61, 383-397.

Repeated injection of pituitary extract (pituitrin) into pregnant rabbits at any time up to and including the 17th day of preg-

nancy, in amounts up to an equivalent of 15 mgm. of moist gland uniformly failed to disturb pregnancy in spite of evidence that other smooth muscle systems were powerfully stimulated. Similar treatment from the 18th to the 29th day of pregnancy never produced immediate abortion but dead fetuses were cast some days later. Progressively smaller doses produced this result on successive days of this period. Upon examination of rabbits killed within a few hours after injection it was found that usually all fetuses were dead and that there were hemorrhages of varying magnitude into the spongy layer of the placenta indicating separation of the latter from the uterus. Injections of successively smaller amounts of pituitary during the period from the 28th to and including the 32nd day, invariably resulted in delivery, complete emptying of the uterus depending on the total amount given. The author concludes that there is no increase in irritability of uterine muscle during pregnancy but an increase in contractility parallel with muscular hypertrophy. Up to the 18th day contractile power is not great enough to cause disturbance of placental attachments, but at this time the threshold is reached for placental injury. The threshold for contractile power sufficient to expel one or more fetuses is reached on the 29th day. It is not believed that there is any increase in pituitary secretion but that the normal amount of secretion can produce expulsion if the contractile power of the uterus is great enough. Early abortion is believed to be due to some disturbance in the hormone control of uterine hypertrophy.

—C. I. R.

Influence of hypophysis feeding on the growth and development
(Weitere Untersuchungen über die Wirkung des Hypophysismus auf die Wachstums und Entwicklungsvorgänge). Krizenecky (J.) & Podhrasky (J.), Arch. f. Entwcklungsmechn. d. Organ. (Leipz.), 1926, 107, 280-298.

Tadpoles (*R. temporaria*) were fed with dried pulverized pars anterior and pars infundibularis of the hypophysis both with and without the addition of algae. Each part with algae gave an increased growth rate; without algae this effect disappeared or was reversed. The pars glandularis caused more of an increase in volume than in length; the pars infundibularis more of an increase in length than volume, and also increased the proportion of ash to body weight. Metamorphosis was hastened by the feeding of both parts of the hypophysis (plus algae) but the authors do not believe that this indicates a specific effect upon metamorphosis but that it results from the increased growth rate. No specific pigmentary effects were seen.—P. E. Smith.

Development of the hypophysis in *Hypogeophis rostratus* (Die Entwicklung der Hypophyse bei *Hypogeophis rostratus*). Laubmann (W.), Ztschr. f. Anat. u. Entwicklungsgesch. (Berl.), 1926, 80, 79-103.

The successive stages of development are illustrated by numerous illustrations of sections and reconstructions. The paper closes with a schema of the anlagen involved in the formation of the hypophysis of fishes, amphibians, reptiles, birds and mammals. Of morphological interest only.—A. T. R.

A case of gravidic diabetes insipidus with great polyuria and probable tubercular lesion of the posterior lobe of the hypophysis (Un caso de diabetes insipida gravidica con poliuria enorme y probable lesión tuberculosa del lóbulo posterior de hipófisis). Marañón (G.), Arch. d. med. Cirugía y Especialidades (Madrid), 1926, 7, 289-293.

A woman with a family history of tuberculosis presented in the third month of pregnancy a polyuria which became accentuated up to the sixth month of gestation with urine amounting to 30 liters in 24 hours. Pituitrin reduced the quantity of urine but only transiently. The medication provoked labor and a living infant was born; it survived 10 days. The skeleton showed fragilitas ossium. The radiograph of the mother showed an elongated sella turcica. In the interior of the sella, near the posterior layer and in the medial plane of the posterior lobe of the hypophysis is shown a calcified spot, the size of a grain of wheat. This case of enormous polyuria is the most exaggerated ever seen by the author. He admits the existence of an old hypophyseal lesion, probably a calcified tubercular lesion, localized in the posterior lobe, with enlargement of the hypophysis and therefore with probable lesion in the centers of the parhypophysis. Gentili has described a very similar case with osteomalacia. These two cases support the theory of intervention of the hypophysis in the beginning of osteomalacia.

—E. B.

The endocrine or neurogenic origin of so-called hypophyseal obesity (Sobre el origen endocrino o neurogenia de la obesidad llamada hipofisaria). Marañón (G.), La Medicina Ibera (Madrid), 1925, 421, 532-535.

The author summarizes the evidence of two theories, maintaining that there certainly exist trophic centers in the parhypophyseal region, but that the direct intervention of the hypophysis in obesity can not be denied. On the clinical side this conclusion is supported by the pathologic anatomy. Thus tumors found in acromegaly are often voluminous and impinge upon the neighboring nerve centers as much as do those found in *Frölich's syndrome*.

But acromegaly is not accompanied by obesity nor by genital hypoplasia save in rare cases in which these are late manifestations superimposed upon the pure acromegaly. The underlying reason is that in acromegaly the tumor represents hyperplasia, whereas in Frölich's syndrome it is of a destructive type. Compression of nervous structures is a common factor. Another argument conclusively in favor of the hypophyseal theory is the existence of adiposo-genital symptoms following destructive lesions (especially hemorrhagic) of the hypophysis without increase in the size of the gland, and hence without secondary involvement of the infundibular centers. The most plausible theory is that the hypophyseal secretion passes, not into the general blood stream, but via the infundibulum to the centers, the activity of which is thereby regulated. This hypothesis has received experimental demonstration from the histological work of Costa, Collin and Vergara Espino.—E. B.

Comparative anatomy of the hypophysis (Zur vergleichenden Anatomie der Hypophyse). Pokorny (F.), *Ztschr. f. Anat. u. Entwicklungsgesch.* (Berl.), 1926, **78**, 308-331.

While largely of morphological interest, some attention is paid to certain physiological phases, such as the significance of the different types of cells and the method of absorption of the secretory substance. In connection with the latter question no evidence was found that the secretion finds its way into the subdural space or into the brain ventricle. The indications are that it passes into the blood vessels.—A. T. R.

Influence of the central nervous system in disturbances of fat metabolism (Beitrag zur Genese centralnervösbedingter Störungen des Fettstoffwechsels). Raab (W.), *Klin. Wchnschr.* 1926, **5**, 1516-1519; *Abst. Physiol. Absts.*, **11**, 557.

Hypodermic injection of pituitrin in dogs causes a fall in the blood fat. Large doses are necessary (5 to 30 cc.), but if injected into a ventricle of the brain small doses (0.2 to 0.6 cc.) will give the same effect. Other autacoids are without action. The pituitrin reaction is prevented by destruction of the infundibulum and tuber cinereum or by division of the cervical spinal cord at the fifth or sixth segment, or by division of a splanchnic nerve. Anterior lobe extracts have no effect on blood fat. The author suggests that the effect of the posterior lobe extracts in reducing the fat content of the blood and causing a fatty infiltration of the liver, as shown by Coope and Chamberlain, is due to the stimulation of nerve cells in the region of the tuber cinereum, and that the pituitary gland in this way is a regulator of fat catabolism. A case of encephalitis of the tuber cinereum and one of syringomyelia in the cervical

spinal cord are described in detail. Both were accompanied by marked adiposity.

Experimental studies on growth. XVIII. Further experiments on the influence of tethelin upon the growth and longevity of the white mouse. Robertson (T. B.) & Ray (L. A.), *Australian Jour. Exper. Biol. & Med. Science* (Adelaide), 1925, 2, 173-188.

Results are reported of experiments on 36 mice. It was found that preadolescent hypodermic administration of tethelin, in dosage of 4 mgm. per day, causes initial retardation, followed by compensatory acceleration of growth, which eventually leads to a considerable overgrowth of the treated animals, which attains its maximum at about 500 days of age. The treated animals then exceed the normals both in size and in weight. The average life-duration of the treated animals exceeded that of the controls by 90 days.

—R. G. H.

Hypophysis and diuresis (Hipofisis y diuresis). Soler (B.) & Pardo, *Los progresos de la Clinica* (Madrid), 1926, 4, 439-474.

A summary of the bibliography with a description of some personal cases and pathological problems of diabetes insipidus. The conclusions are as follows: The hypophysis and the tuber cinereum form a mechanism which regulates diuresis; diabetes insipidus depends on conditions in these structures jointly; the hypophysis functions by producing a hormone which acts upon the tuber cinereum and likewise via the circulation upon the kidneys; lesions of the tuber centers cause diabetes insipidus (very common); lesions of the posterior lobe of the hypophysis cause diabetes insipidus (many cases); the activity of the hypophysis upon the centers is not direct but hormonal. In the present state of our knowledge to deny participation of the hypophysis in the pathogenesis of diabetes insipidus is not justified.—E. B.

Pituitary etiology of diabetes insipidus. Straemmler (M.), *Klin. Wchnschr.*, 1924, 3, 1799.

The author discusses the etiology of diabetes insipidus. Two views are held: (1) cerebral, due to injury to midbrain, of which Leschke is the chief exponent; (2) hypophyseal with the lesion of the posterior lobe and pars intermedia associated with hypofunction. Schäfer and Herring are adherents to this theory. An autopsy was made of a patient who died of sarcoma of the brain with complete destruction of the posterior lobe and pars intermedia of the hypophysis. The anterior lobe was not penetrated by the tumor, but was necrotic in areas. Cross sections of the base of the brain and infundibulum showed involvement of the latter and progressive impairment of the base of the brain. Diabetes insipidus had mani-

fested itself at the beginning of the illness. It is possible that it existed prior to the involvement of the midbrain, and appeared when only the posterior and middle lobes of the hypophysis were disturbed. He emphasized the point that there are many cases in literature in which diabetes insipidus was absent in spite of a far-reaching destruction of the hypophysis, and also in which it abated before termination of the illness. Staemmler advanced the opinion that to produce the state of diabetes insipidus together with hypofunction of middle and posterior lobes of the hypophysis the anterior lobe must remain unimpaired. The abatement of the diabetes insipidus he attributes to a disturbance of the blood supply, resulting in anemia and later necrosis of the anterior lobe. The recurrence of diabetes insipidus is due to the fact that the necrosis is not complete and the preserved glandular cells recover and begin functioning. Shortly before death renewed circulatory disturbance causes the anterior lobe to stop functioning and diabetes insipidus ceases.

—H. G. Beck.

The effect upon amphibian differentiation of feeding iodo fibrin, iodoedestin and iodogliadin. Swingle (W. W.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, **24**, 205-206.

Iodo fibrin fed to 30 mm. frog tadpoles that had been hypophysectomized produced metamorphosis in 24 days. Operated controls fed non-iodized fibrin did not metamorphose. Similar animals fed iodoedestin and iodogliadin took 90 days to reach the same stage that iodo fibrin fed tadpoles reached in 20 days.—J. C. D.

Surgery in diabetics. Alexander (E. G.), Atlantic M. J. (Harrisburg), 1925, **28**, 674-680.

This is a useful survey of situations of surgical nature as they arise in diabetic patients, with suggestions in treatment. Alexander urges a routine examination of all obese patients admitted to the surgical ward of a hospital, stressing particularly the need for blood sugar estimations.—I. B.

The action of pancreas extirpation followed by thyroidectomy on the sensitivity of dogs to insulin (*Die Wirkung der Pankreasextirpation und der darauf folgenden Thyreoektomie auf die Empfindlichkeit von Hunden gegen Insulin*). Aszodi (Z.) & Ernst (Z.), Arch. f. d. ges. Physiol. (Berl.), 1927, **215**, 431-442.

In normal animals the blood-sugar curve after injection of a powerful dose of insulin reaches its lowest value at the end of the third hour. This time-period bears no close relationship to the amount of insulin injected. In depancreatized dogs the minimum value for the same dose of insulin is not reached before four to five hours. A close parallelism between dose and action is observable.

Thyroidectomized dogs are more sensitive to insulin than normal animals, and the sensitivity of depancreatized dogs is increased after removal of the thyroid.—A. T. C.

Diabetes mellitus: An experimental study on the etiology of the disease. Bergey (D. H.), *Proc. Soc. Exper. Biol. & Med. (N. Y.)*, 1926, 24, 229-232.

Urine from diabetic rabbits and from a patient with diabetes was passed through a Berkefeld filter and then injected into rabbits. These rabbits showed sugar in the urine after variable periods. This suggests that diabetes is caused by an ultra-microscopic organism.—J. C. D.

Acidosis, coma and infections in diabetes mellitus. Campbell (W. R.), *Internat. Clin. (Phila.)*, 1926, (Series 36), 4, 3-16.

This is an excellent review of the subject. In the past four years the economic value of human life and suffering saved by insulin has become almost incalculable. But much further work, both clinical and experimental, is required to solve the riddle of carbohydrate metabolism. There is little hope of a patient diagnosing acidosis early except by the use of the Gerhardt ferric chloride reaction for aceto-acetic acid in the urine. Patients should be taught to report a positive test to their physician and to adopt measures against acidosis immediately. Infections very likely diminish the production of insulin and decrease its effectiveness. Since it is easier to prevent coma than to cure it, it is advised that severe ketonic acidosis be treated vigorously. The treatment of coma is similar to that of acidosis, but the urgency is greater. Hospital treatment for these cases is most desirable, but they should receive 60 units of insulin immediately the diagnosis is made and then brought to the institution. Patients arriving at the hospital who were previously untreated for the comatose state should receive insulin at once. It is necessary to administer ten times the dosage to double the rate of action of insulin, hence small doses may be futile. One hundred units intravenously is not an excessive dose under the circumstances. Many cases of abdominal distress vaguely diagnosed as indigestion or gall bladder infections are really instances of pancreatitis in subacute form. In patients finally sugar-free, glycosuria may develop with the onset of tonsillitis, laryngitis and other infections. Pyogenic infections do not often produce glycosuria unless the pus is confined. It is not uncommon for a mild diabetic suddenly to acquire all the characteristics of typical diabetes with the onset of an infection. No patient requiring surgical treatment need be refused operation because of diabetes. There is now no mortality from diabetes itself in surgery, assuming, of course, that two days' time are taken in freeing the

patient of acidosis and putting glycogen into his liver by means of diet and insulin treatment. The choice of an anesthetic is important, and nitrous oxide oxygen, intrathecal or paravertebral anesthesia are to be preferred.—I. B.

Experiments on diabetes and insulin action VI. The antagonistic action of diabetic plasma to insulin (*Untersuchungen über Diabetes und Insulinwirkung. VI. Ueber die insulinantagonistische Wirkung des diabetischen Plasmas*). Dietrich (S.), *Arch. f. d. ges. Physiol. (Berl.)*, 1926, **214**, 675-677.

The inhibition of red-cell uptake of glucose by diabetic plasma is due to some chemical action and not to a physical-chemical condition, since the dialysate of the plasma is active in producing the effect as is also the alcoholic extract of a dialysate concentrated at 100° C. The ash from the dialysate is inactive.—A. T. C.

Experiments on diabetes and insulin action VII. (*Untersuchungen über Diabetes und Insulinwirkung VII.*). Dietrich (S.) & Loewi (O.), *Arch. f. d. ges. Physiol. (Berl.)*, 1926, **215**, 78-94.

Insulin acts first through structural fixation of glucose, and thereby, secondarily through promotion of change of glucose. In diabetes an insulin-antagonist is produced which inhibits these actions.—A. T. C.

The preparation and management of the surgical diabetic. Duncan (G. G.) & Frost (I. F.), *Surg. Gynec. & Obst. (Chicago)*, 1927, **44**, 253-260.

Diets high in carbohydrate and low in fat and total calories should be used for preparation for operation, and during the active stage of healing the total calories should be restricted to at least a maintenance level. Insulin should be given immediately before operation, and glucose injected intravenously immediately after, to prevent ketosis and vomiting. The blood-sugar should as far as possible be kept normal throughout treatment.—A. T. C.

Recent studies of diabetes in children. Geyelin (H. R.), *Atlantic M. J. (Harrisburg)*, 1926, **29**, 825-830.

The progress of diabetic children at present offers much encouragement as to the eventual outcome. In the case reported by Boyd in which, after the continuous use of insulin for nearly two years, the patient was accidentally killed, the autopsy revealed definite evidence of regeneration of the islands of Langerhans. The insulin-treated child is still a potentially severe diabetic, but on the whole, progress in the majority of instances has occurred, and mental and physical development has taken place in a qualitatively

normal manner. In the author's series of 51 insulin-treated diabetic children, there have been but four deaths in three years. None of these deaths could be attributed to diabetes. Generally speaking, the improvement of diabetic children on higher carbohydrate and lower fat diets has been more satisfactory than in the lower carbohydrate and higher fat diets.—I. B.

The effect of pancreatic extract upon cardiac contraction (*Acerca de la acción reforzadora de los extractes pancreáticos sobre la contracción cardíaca*). Guerra (H.), *Arch. d. Cardiol. y Hematol.* (Madrid), 1926, 3, 101-110.

The author has shown that the administration of pancreatic extract causes augmentation of the amplitude and frequency of the heart beat.—E. B.

Insulin and arterial blood pressure (*Über die zweiphasische Wirkung des Insulins auf den Blutdruck*). Hahn (L.), *Klin. Wchnschr* 1926, 5, 1429; *Abst. Physiol. Absts.*, 11, 549.

Hypodermic injection of 5 to 10 units of insulin into a normal person causes an immediate rise of arterial pressure followed by a fall after 20 to 30 minutes, to a level lower than the original. In diabetic subjects this is not observed. The author attributes the rise in blood pressure to a liberation of adrenalin which is produced by insulin.

Experiments on diabetes and insulin V. (*Untersuchungen über Diabetes und Insulinwirkung*). Häusler (H.) & Loewi (O.), *Arch. f. d. ges. Physiol.* (Berl.), 1926, 214, 370-379.

The glucose uptake by red cells following insulin injection is less when the insulin has been previously treated by dilute alkali.

—A. T. C.

The blood sugar in diabetes in pregnancy. Holzbach (E.), *Zentralbl. f. Gynäk.* (Leipz.), 1926, 50, 2610; *Abst. J. Am. M. Ass.*, 88, 288.

Holzbach describes a case in which, in a diabetic woman, aged 29, the death of the fetus in the thirty-sixth week of pregnancy was followed immediately by a rise of the mother's blood sugar from 120 to 224 mgm. per hundred cubic centimeters. The sugar in the urine increased to 44.8 gm. in 24 hours, and the patient became gravely ill; coma, however, did not develop. Insulin was not given. The next day a dead child, weighing 4,250 gm., was delivered in a markedly macerated condition. The mother's blood sugar was 265 mgm. per hundred cubic centimeters. Insulin treatment was now started and the patient responded promptly. She was under observation for the next two weeks. She showed a certain hypersensitivity to insulin and frequently became hypogly-

cemic. The urine was sugar-free on her discharge, but the blood sugar still exceeded 200 mgm. per hundred cubic centimeters if insulin treatment was interrupted. Holzbach places this case, in which a compensated diabetes was suddenly converted into an uncompensated one by the death of the fetus, beside the animal experiments of Carlson and Ginburg, in which removal of the pancreas from pregnant dogs did not cause hyperglycemia or glycosuria so long as the living fetus remained in the uterus. His conclusions are that, in the later weeks of pregnancy at least, the fetal pancreas gives out a hormone which takes part with the maternal hormone in carbohydrate metabolism and is able to protect the mother in case of diabetes. In the case here described, the fetus might have continued to live had not the intake of calories been considerably and suddenly raised in an effort to combat inanition in the mother. Holzbach urges the use of insulin in the attempt to keep the fetuses of diabetic mothers alive.

Hyperinsulinism. John (H. J.), Surg. Gynec. & Obst. (Chicago), 1927, 44, 190-193.

Symptoms of hyperinsulinism are so like those of hyperthyroidism that it is difficult to make a differential diagnosis without a blood-sugar examination. Urine analysis is insufficient to establish insulin control in diabetes, on account of the possibility of a low renal threshold. A sugar tolerance test is necessary or else hyperinsulinism may result.—A. T. C.

Action of insulin on the disappearance of glucose and oxidations in the blood in vitro (*Action de l'insuline sur la disparition du glucose et les oxydations dans le sang in vitro*). Kauffmann-Cosla (O.) & Roche (J.), Bull. soc. chim. biol., 1926, 8, 636-654.

Blood was obtained aseptically from the vessels of the pig and defibrinated. The addition of insulin sharply increased glycolysis and the production of carbon dioxide, though there was no correspondence between the amounts of the two produced. The action of insulin on the production of carbon dioxide was not affected by cyanide. Glycolysis and production of carbon dioxide diminish spontaneously in blood in vitro. Addition of insulin to blood that had been kept 5 hours at 0° C. restored both processes to normal rate, suggesting that insulin is normally present in blood and decomposes spontaneously in vitro. Red cells, washed, and suspended in Ringer-glucose solution, in presence of insulin bring about a definite disappearance of glucose, though the insulin does not affect the production of carbon dioxide. Since it is known that acetaldehyde is produced by insulin action the results suggest that insulin action results in the breakdown of glucose.—A. T. C.

The pancreatic-suprarenal antagonism in physiology and in the clinic (*El antagonismo pancreático-suprarrenal en fisiología y en clínica*). Marañón (G.), *Actualidad méd.* (Granada), 1925, 12, 423-429.

There is undoubtedly a physiologic and a pathologic antagonism between the endocrine functions of the pancreas and the suprarenals. Independent of the disturbances of the other factors which regulate fat metabolism, the equilibrium of the metabolism is destroyed by the disturbance of these two factors which are fundamental. Of the four theoretical syndromes of pancreatic and suprarenal disturbance two are certain: the hypopancreatic or the hyperglycemic (diabetes) and the hypoadrenalinic or hypoglycemic (Addison's disease). The other two theories are: the hyperpancreatic or hyperinsulinic and the hyperadrenalinic which are produced experimentally by injections of insulin and of adrenalin, respectively. In clinical cases, however, these two conditions are not found.—E. B.

Pancreatic diabetes and pregnancy. Markowitz (J.) & Soskin (S.), *Am. J. Physiol.* (Balt.), 79, 553-558.

The carbohydrate balance remained unchanged from day to day during pregnancy in a depancreatized dog treated with insulin. In two dogs which were depancreatized during the later stages of pregnancy and given small doses of insulin the diabetic symptoms as judged from the behavior of the blood sugar, the D:N ratio and R.Q. were as severe as would be expected after pancreatectomy in non-pregnant animals. There is therefore no evidence that the fetal pancreas can secrete into the maternal organism a sufficient amount of insulin to offset the diabetic condition caused by pancreatectomy. The mammary glands in all three animals failed to hypertrophy properly.—Author's abstract.

The pre-operative preparation of the diabetic patient with discussion of the "so-called" diabetic gangrene. Mason (E. H.), *Canad. M. Ass. J.* (Montreal), 1927, 17, 23-26.

Mason considers that in a clinic well organized for the handling of diabetic cases with correct use of insulin and dieting their mortality should be very little, if any, above that of the non-diabetic.
—A. T. C.

The use of insulin by mouth. Miller (H. R.), *Arch. Int. Med.* (Chicago), 1926, 38, 779-784.

Inasmuch as the parenteral use of insulin has obvious disadvantages, a method for its oral use would be valuable. Accordingly, the author administered by mouth gelatin capsules, dipped in

7% glacial acetic acid keratin solution, containing concentrated insulin (Lilly) in absolute or 95% alcohol (it is important to use not more than 3 minims of insulin to each 1 cc. of alcohol). By this method varying doses of insulin were given to diabetic and non-diabetic patients. The blood sugar of diabetic patients was greatly lowered (illustrated by graphs and figures in this article). Although it is not always possible to determine the content of which or how many keratinized capsules is absorbed, nevertheless the results of this investigation suggest that insulin given by mouth depresses the hyperglycemia of diabetic patients.—Author's abstract.

Modern views on the Vichy treatment of diabetes. Monod (G.), Internat. Clin. (Phila.), 1926 (Series 36), 2, 103-110.

A comparison is made between the Vichy Spa treatment of diabetes on the one hand and the dietetic treatment on the other. The Vichy treatment is indicated in intermittent diabetes, simple diabetes and enlargement of the liver (florid type of diabetes), diabetes with dyspepsia and lithiasis, gouty and uricaemic diabetes, glycosuria of toxic origin, and diabetes in children with distinct hepatic disturbances. For a treatment to be really successful three persons play an important part: The family doctor, the Spa doctor and the patient himself. Other factors which must not be lost sight of are the physical, mental and moral rest and quiet which patients enjoy during their stay at Vichy. We have already learned to guard against the enthusiasms raised when the results of urine analysis become very favorable. Diabetes cannot be cured by a twenty-one days' cure at Vichy when for the rest of the year the patient indulges in dietetic eccentricities. Vichy treatment is not indicated in the diabetes with emaciation frequently observed in children, but even in these cases it is useful against the hepatic symptoms often associated with diabetes. Vichy is of no avail or at best can give but a very temporary improvement in cases of diabetes with progressive loss of weight, marked acidosis, cachexia, or tuberculosis.—I. B.

Basal metabolism in human diabetes (II metabolismo basale nel diabete umano). Poggio (G.), Gior. di Clin. med. (Parma), 1926, 7, 2-19.

Basal metabolism was studied in seven cases. In general it was diminished, but was found to show considerable variations with the changing of very numerous conditions.—P.M.N.

Diabetic gangrene. Rabinowitch (I. M.), Canad. M. Ass. J. (Montreal), 1927, 17, 27-35.

A study of 1000 diabetics showed that 3.5% had gangrene. Of these, two-thirds were males, though the incidence of diabetes was

equal for the sexes. The incidence increases with age; about 25% of all diabetics over 70 years old develop gangrene. The average blood cholesterol content of 16 diabetics with gangrene was 0.344%. The average for 16 non-diabetic arteriosclerotics with gangrene was only 0.249%, suggesting two different forms of gangrene. There is a greater incidence of gangrene on the left foot and it is suggested that this is due to its greater accessibility to right-handed people.

—A. T. C.

Cholesterin in diabetes and the influence of insulin (*La colesternemia en la diabetes y su influencia por la insulina*). Serraller (F. E.), Arch. d. Endocrinol. y Nutrición (Madrid), 1925, 3, 362-375.

The author has determined the cholesterin before and after the treatment of insulin in 17 diabetics, obtaining a mean value of 2.75 per 1000. In many cases considered singly, there is found no relation between the cholesterin and the glycemia. In one case there could be determined coexisting factors which acted directly upon these two phenomena, increasing the intensity of one and diminishing the other. In conjunction with the observations, however, there was found a relation between the grade of hyperglycemia and that of cholesterin. Insulin always determined a greater or lesser fall in grade of cholesterin in the blood. The author considers it indubitable that insulin acts upon hypercholesterin in the diabetics with the same certainty and strength as upon hyperglycemia.—E. B.

The effect of insulin on blood cholesterol, fat and sugar in nephrosis. Shih-Hao (L.) & Mills (C. A.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 24, 191-192.

Insulin reduced temporarily the cholesterol and fat in blood of three nephritics but did not influence the amount of blood sugar.

—J. C. D.

Insulin in cardiac insufficiency in a pregnant diabetic with acidosis (*La insulina en una insuficiencia cardiaca en una diabetica embarazada con acidosis*). Soler (B.), Arch. d. Endocrinol. y Nutrición (Madrid), 1926, 2, 57-68.

In a pregnant diabetic with acidosis and cardiac insufficiency refractory to all medication the use of insulin produced a great improvement. The most interesting result was that the heart which was weakened by the illness, the disability being so severe as to raise the question of therapeutic abortion, became normal in the last months of pregnancy and childbirth was normal. This effect is explained by the author as due to three causes: freeing of the heart from acidosis intoxication, the power to take nourishment

(effect of insulin upon the vagus), as shown by the experiments of Starling. A heart of a diabetic, isolated and irrigated with the subject's own blood does not consume glucose; but if to the perfused liquid pancreatic substance is added it fixes and consumes the glucose. In the case of the author there existed a heart which utilized glucose poorly. Insulin acted as a mordant, fixing the sugar in the myocardium; at the same time acidosis disappeared and the cardiac function was restored.—E. B.

The behavior of hepatic glycogen in fasting animals treated with insulin. Visco (S.), *Atti accad. Lincei*, 1926, 4, 153-160; *Abst. Chem. Absts.*, 21, 257.

The administration of insulin to fasting rabbits diminished the loss of weight occurring among those of the same strain, weight and sex. After five days' fasting the weight of the liver and of the spleen when given insulin were greater than the weight of those of normal animals, whereas the heart, kidneys, adrenals and lungs showed only slight differences. From the liver after five days' fasting, with administration of insulin, was extracted by the Pflüger method 1.10-1.90 gram of glycogen per 100 grams of fresh liver, while from the liver of animals, under identical conditions, but not given insulin, was extracted a maximum of 0.521 gram of glycogen per 100 grams of liver.

Arginine and its possible relation to the physiological activity of insulin. Sandberg (Marta) & Brand (E.), *Proc. Soc. Exper. Biol. & Med.* (N. Y.), 1927, 24, 373-376.

Insulin gives color reactions for arginine. Insulin subject to enzymatic hydrolysis gives 12% arginine. The physiologic activity of insulin seems to be associated with arginine. This suggests that insulin acts through the nervous system and therefore that insulin reactions cannot be reproduced in a test tube.—J. C. D.

The internal secretion of the parathyroid glands. Collip (J. B.), *Internat. Clin.* (Phila.), 1926 (Series 35), 3, 77-80.

This is a report on the active principle of the parathyroids. By weak acid hydrolysis of the fresh glands of the ox an extract was obtained by the use of which tetany was prevented or controlled in dogs which had had the parathyroid glands removed. A great difference was noted in the effect of the potent extract upon different species of animals. Rats and rabbits were peculiarly resistant to the hormone, and overdosage phenomena have not been observed in these animals. It would appear that the dog is the animal of choice for physiological standardization of the parathyroid hormone. It was also shown that the administration of the potent

extract to dogs with a low blood serum calcium caused the calcium content of the serum to be increased. The specific effect of the extract in relieving the tetany, and the blood serum calcium mobilizing effect, were found to run parallel. Marked physical as well as chemical changes were also noted in the blood, particularly in the preterminal stage. These changes consisted of increased viscosity, decreased plasma volume, and decreased clotting time. The subcutaneous administration of the hormone to the human individual causes a mobilization of calcium in the blood. That it will be a useful therapeutic agent in parathyroid deficiency there can be little doubt. It has already been used with good results in both acute and chronic cases of tetany of parathyroid origin. It is possible that further clinical study may indicate that through its profound effect on calcium metabolism other uses may be found for it. It is a fact of great importance that proteolytic enzymes, such as pepsin and trypsin, completely inactivate the extract. It is obvious, therefore, that the extract should be given by injection if results are to be obtained. As previous investigators have used acid extracts of the parathyroid gland, the chief advance which the present work represents is in the matter of the clean-cut proof of the specific physiological effect of the parathyroid hormone, in the development of a method of physiological assay, and in the purification and stabilization of the active principle.—I. B.

Blood chemistry in parathyreoprival tetany. Its treatment by the Dragstedt method. Frank (E.), Haring (W.) & Kühnau (J.), *Arch. f. exper. Path. u. Pharmakol.* (Leipz.), 1926, **115**, 48-54; *Abst., Chem. Absts.*, **21**, 609.

Hypoglucemia is never encountered in any stage of parathyreoprival tetany. The calcium of the serum is reduced to 50% of its normal value, and the phosphate of the blood is usually increased while that of the urine is reduced. As a rule the actual reaction of the blood is not changed, although in the acute stage there is a shift toward the acid side.

The effect of long continued administration of parathyroid extract upon the excretion of phosphorus and calcium. Greenwald (I.) & Gross (J.), *J. Biol. Chem.* (N. Y.), 1926, **68**, 325-333.

With the intention of simulating possible clinical cases of hyperparathyroid function, parathyroid extract (Collip) was administered to a dog weighing 6.8 kg. for a period of 52 days, and, after a rest of 19 days, for another period of nine days. Administration was suspended as soon as the dog refused food. The diet was constant and was poor in calcium. During the control periods, the loss of calcium was 0.012 grams per day. The administration of parathyroid extract increased this by an average of 0.045 grams per

day, or a total of 2.75 grams. The total loss of calcium in the 99 days of the entire experiment was 3.94 grams. The increased excretion of phosphorus was approximately half as great. The calcium and phosphorus must have been derived from the bones.

—I. Greenwald.

A case of maternal tetany relieved by parathyroid extract—Collip. Lissner (H.), Smith (R. K.) & Shepardson (H. C.), J. Am. M. Ass. (Chicago), 1927, **88**, 461-463.

In a case of tetany immediately post partum it is shown that, while the supply of available calcium was in all probability normal, the loss of some 1,500 cc. of blood induced marked symptoms of hypocalcemia (cesarean section had been performed because of placenta praevia marginalis). The prompt administration of active parathyroid hormone—Collip in adequate dosage, without the aid of any other therapeutic agent, even calcium, relieved the hyperexcitability of the nervous system and caused the calcium content of the blood serum to return to normal (from 7.5 to 9.7 mgm. per 100 cc.). This case offers therapeutic substantiation of the parathyrogenous origin of maternal tetany.—Author's abstract.

Parathyroid hypercalcemia and anaphylactic shock. Levinson (S. A.) & Mathews (S. A.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1927, **24**, 350-351.

Collip's parathormone was tested on eight dogs to see if it would reduce the effects of anaphylactic shock. It had no influence.—J. C. D.

Morphology of the parathyroid gland in Anura (Morphologische und experimentelle Studien über die Epithelkörper der Amphibien. I. Teil. Die Morphologie der Epithelkörper der Anuren). Romeis (B.), Ztschr. f. Anat. u. Entwicklungsgesch. (Berl.), 1926, **80**, 547-578.

Largely of morphological interest. The author describes cyclic changes from a rather solid epithelial parenchyma to a reticular phase with highly vacuolated cells containing a non-fatty and protein-poor fluid. As a result of cell division this stage gradually returns to the more compact stage.—A. T. R.

The prevention of tetany by the oral administration of ammonium chloride. Wenner (W. F.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, **24**, 210-211.

Parathyroidectomized dogs can be carried through the dangerous period following this operation and in favorable cases to complete and permanent freedom from tetany by giving ammonium chloride by mouth.—J. C. D.

On some anatomical changes which follow removal of the pineal body from both sexes of the immature albino rat. Izawa (Y.), *Am. J. Physiol. (Balt.)*, 1926, **77**, 126-139; *Abst. Physiol. Absts.*, **11**, 557-558.

The gland was removed from the animal at 20 days of age; the operation was performed under ether, and the pineal plucked out with forceps through an opening in the parietal bone. Complete removal resulted in accelerated growth in both sexes, affecting body length, and especially body weight, over the period of 65 days before the animals were killed; comparison was made with controls from the same litter. The operation alone was not responsible for this result. In complete removal a slight retardation of growth was observed. As regards the individual organs, the following showed variations from the normal which were statistically significant: eyes, decrease in weight about 5%; gonads, increase in weight of about 25%; pituitary, decrease in weight, in females only, of 15%.

Action of splenic extracts on the blood corpuscles (*Sull'azione degli estratti splenici esplicano sugli elementi corpuscolati del sangue*). Bisceglie (V.), *Biochim. e terap. sper. (Milano)*, 1925, **12**, 201-224.

The author investigated the problems whether splenic extract is hemolytic; if so, whether it is active in vitro; what are the properties of this substance; its effect on leucopoiesis. The extracts are prepared by Dodds and Dickens method for insulin. There are reported 19 experiments on rabbits and dogs, and very numerous in vitro tests. The hemolyzing substance is thermostable. It shows the paradoxical phenomenon previously observed by Sachs for the saponine, i. e., that normal serum prevents the hemolysis, but when it is added to red corpuscles that have already been treated with sub-threshold quantities of the hemolytic substance, then it causes hemolysis. In about ten experiments the splenic extract gave a general leukocytosis, the lymphocytes being relatively most numerous. This indicates, not a general reaction to protein, but a specific effect.—P. M. N.

Clinical Manifestations of Enlarged Thymus. Morgan (E. A.), Rolph (A. H.) & Brown (A.), *J. Am. M. Ass. (Chicago)*, 1927, **88**, 703-706; *Abst. A. M. A.*

The clinical manifestations in fifty-four cases of enlarged thymus are reviewed. In two cases, enlargement of the thymus was discovered accidentally and was unaccompanied by symptoms, but in the remaining fifty-two attention was directed toward the gland by the presence of suggestive manifestations. Holding-breath spasms were recorded in twenty-nine cases. Syncope occurred in nine

cases; cyanosis in eight cases; cough in seven cases. Persistent hoarse cough was the principal complaint in four, and in the remainder it was of secondary importance. Noisy nasal breathing was the chief symptom in six cases; choking attacks, in five cases. Typical thymic asthma commencing at or shortly after birth, and characterized by marked dyspnea, prolonged and difficult inspiration, retraction of the soft parts on inspiration and cyanosis was present in only three cases. In one, the clinical picture was somewhat confused by the occurrence of tongue-swallowing, which helped to aggravate the dyspnea. In another instance, the attacks of cyanosis and dyspnea were precipitated by hyperextending the baby's head or by doubling up the body. Rapid, panting respiration was a symptom in four cases. Nervous manifestations, such as sleeplessness, restlessness and irritability, were reported in three instances to have disappeared following roentgen-ray therapy. Twelve, or 22% of the patients, suffered from eczema, either localized or general. Roentgen-ray therapy proved efficacious in relieving the symptoms in 96% of these cases. Recurrence of thymic enlargement or of clinical manifestations has been noted in twelve of the cases. In all these instances, further roentgen-ray therapy resulted in complete recovery.

The function of the thymus gland. Goldschmidt (S.), Atlantic M. J. (Harrisburg), 1926, 29, 852.

Up to the present time investigators have been unable to bring to light, unchallenged, any specific rôle which may be ascribed to this organ. Indeed, it is significant that many writers, endocrinologists included, are frankly doubting whether it may be classed as an endocrine gland. Such is the case in spite of the fact that much research on the thymus has been done and many important bodily functions have been attributed to it.—I. B.

Thymic death in an adult during tonsillectomy under local anesthesia. Husik (D. N.), Atlantic M. J. (Harrisburg), 1926, 29, 857-859.

This exceedingly interesting case has led the author and others to radiograph the chest of all patients who are candidates for tonsillectomy—children as well as adults. The patient was a woman of 20, whose tonsils were markedly enlarged and infected. She was given $\frac{1}{2}$ grain of morphin sulphate and $\frac{1}{150}$ grain atrophin sulphate hypodermically a half hour before operation. With the patient in the sitting posture, the anterior faucial pillars were touched with a few drops of 10% cocaine solution. Four cc. of $\frac{1}{2}$ % novocain solution plus 4 drops of 1:1000 adrenalin solution were injected through the anterior pillar back of the capsule at about the junction of the upper and middle thirds. The patient

became greatly excited and the left tonsil was rapidly removed. She then began to stiffen with short clonic convulsions. She then lost consciousness, became cyanotic, respirations became irregular and shallow and the pulse feeble. Strychnine sulphate 1/30 grain, was given, but respirations soon stopped, the pulse continuing for a short time afterward. Intracardiac injections of 4 cc. of adrenalin solution, 1:1000, were given without avail. The whole attack from the time of the novocain injection to the time of cardiac arrest was four minutes. Artificial respiration was continued for 20 minutes but without effect. Post-mortem examination revealed marked thymus hyperplasia. Death during tonsil operation in an adult with a large thymus as the apparent cause is an exceedingly rare occurrence.—I. B.

Development of foetal thyroid and pancreatic islets (*Evolution de la thyroïde foetale chez les mammiferes. Sa concordance avec l'évolution du pancreas endocrine*). Aron (M.), *Compt. rend. Soc. de biol. (Par.)*, 1926, 94, 275; *Abst. Physiol. Absts.*, 11, 621.

The work has been done principally on the sheep, but the calf, guinea-pig, and man have also been used. In the sheep colloid appears when the embryo is 9 cms. long, and persists till the length is 15 to 19 cms. At this stage the cells are low and vesicles swell, enclosing a dense colloid. The colloid is then rapidly replaced by a coagulable fluid. The reversal of the Golgi apparatus has never been observed. The beginning of these phenomena corresponds exactly with the development of the islets of Langerhans. The stages of development of the islets differ in different species, but are always found to synchronize with the changes described in the thyroid.

Biological control of antithyreokrin (*Zur biologischen Kontrolle des Antithyreokrins*). Asimoff (G.), *Arch. f. d. ges. Physiol. (Berl.)*, 1926, 215, 191-196.

"Thyreokrin," a thyroid preparation of the Endocrinological Institute of Moscow, is prepared from thyroids by consecutive extraction with 96% alcohol and benzine, the residue being dried at 20-22° C. "Antithyreokrin" is analogous to "antithyreoidin" prepared from the blood of a goat thyroidectomized 1.5 months previously and showing marked symptoms (*deutliche Symptome der Thyreidektomie*). The blood is coagulated in a thermostat, then kept for 24 hours on ice, the serum poured off, centrifuged, evaporated at 18° C. in 1.5 hours, and powdered. Antithyreokrin in combination with thyreokrin delays the thyroid action on metamorphosis of axolotls. In ratio of 10:1 the delay is marked; in ratio of 20:1 it is completely hindered. Antithyreokrin itself is without action on the axolotl.—A. T. C.

Sudden atmospheric changes as contributory factors in the production of tetany. Cameron (A. T.) & Carmichael (J.), Roy. Soc. Can. (Ottawa), 1926, 20, Sect. V, 277-396.

The possibility of an onset of tetany from a summation of different causes is emphasized. When young rats are fed thyroid for a week or longer their serum calcium tends to be diminished, presumably through a sub-parathyroidism resulting from decreased circulation to the thyroid-parathyroid apparatus. Diminished oxygen tension rapidly induces tetany in such animals, the rapidity of onset of convulsions depending on the degree to which pressure is diminished. Normal animals are similarly but more slowly affected. This tetany is considered due to an alkalosis following 'over-ventilation'; in thyroid-fed rats this accentuates the effect of an existing plasma-calcium deficiency, and therefore produces an earlier effect. A large percentage of the thyroid-fed rats who under otherwise normal conditions develop tetany do so during or following a sudden fall of barometric pressure. This fact is similarly interpreted. It is suggested that the greater incidence of tetany in the Spring months in continental climates is due to a fall of barometric pressure, accompanied by sudden marked rises in humidity and temperature, a combination which is not uncommon at this period of the year, and which additively leads to diminished oxygen tension, resulting in a mild alkalosis that accentuates a latent tetany condition due to some other cause.—A. T. C.

An attempt to evaluate thyroid preparations, utilizing their effect on growth-rate and production of organ-hypertrophy in the young white rat. Cameron (A. T.) & Carmichael (J.), Tr. Roy. Soc. Can. (Ottawa), 1926, 20, Sect. V, 1-17; the relative activity of thyroid fractions and derivatives, *Id.* 307-319.

The effect on growth-rate of the test-animal is measured as the increase in weight of the control minus that of the test animal, divided by the increase in weight of the control minus that of a rat fed a standard dose. The effect on heart, liver, and kidney is similarly measured in each case as the corrected percentage organ weight of the test animal minus the percentage organ weight of the control, divided by the corrected percentage organ weight of the rat fed the standard dose minus the percentage organ weight of the control. Using the means of these four measurements it is shown that the results of a series of dosages of a standard thyroid preparation (fed daily, and based on body weight) conform to the equation $y = \log(x + 1)$ where x is proportional to the thyroid-iodine dose, and y is the mean effect. Eleven different thyroid preparations were tested by this method. Seven (whose iodine content varied from 0.1 to 0.39%) gave for the same thyroid-iodine dose an effect of the same order of magnitude within the limit of error of the

method, two beef and one sheep preparation gave definitely lower effects, and the eleventh a possibly greater effect.

It was also found by this test that thyroglobulin prepared by Oswald's procedure, and dried without the use of heat, contained the full activity of thyroid, based on iodine content, but thyroxine does not appear to do so. Diiodotyrosine is inactive. Enzymic hydrolysis does not destroy the activity of thyroid. A solution has been obtained from the enzymic hydrolysis of thyroglobulin which can contain but a trace of thyroxine but which is still distinctly active. Hydrolysis of thyroglobulin by sodium hydroxide gives an active thyroxin fraction and an inactive acid-soluble fraction. Water extracts of thyroid show negligible activity.—A. T. C.

Physical examination and determination of basal metabolic rates of a group of young adults (medical students and nurses). Cameron (A. T.), Kitchen (H. D.) & McRae (D. F.), *Canad. M. Ass. J.* (Montreal), 1926, **16**, 1201-1205.

Of 193 male students examined 92 were functionally and physically perfect, and 113 functionally normal. The most frequently occurring abnormality was slight thyroid enlargement. The nurses could not be regarded as an unselected group. With them slight thyroid enlargement was the only abnormality. The basal metabolism figures of 110 normal males and 57 normal females of ages varying from 18 to 32 years are in agreement with the DuBois and Benedict standards. The "Sanborn" tables at present in use are 5% too high for adults of these ages, and may lead to error if employed clinically. Read's formula for calculation of basal metabolic rate from pulse pressure and pulse rate has been tested with a group of normal and pathological individuals and the results do not justify the clinical use of this formula.—A. T. C.

The clinical value of adrenalin in thyroid conditions (*La investigación de la adrenalin en los estados tiroideo y su valor clínico*). De Lucas (C.), *Arch. d. Endocrinol. y. Nutrición* (Madrid), 1925, **3**, 249-279; 325-361.

The sensitivity to adrenalin is modified in thyroid conditions and is roughly parallel to the activity of the thyroid. Evidence of this is shown by the technic of Csepai. Of the many modifications produced by the injection of insulin, that which is the most practical for clinical use is the tensional reaction.—E. B.

The surgical treatment of goitre. Fahrni (G. S.), *Canad. M. Ass. J.* (Montreal), 1926, **16**, 1188-1194.

A general review with several case reports. The change in the histological appearance of the thyroid after administration of

Lugol's solution is emphasized, there being marked increase of lymphoid infiltration.—A. T. C.

The influence of thyroid hormone on phagocytosis (*Zur Frage der Beeinflussung der Phagocytose durch das Hormon der Schilddrüse*). Fleischmann (W.), *Arch. f. d. ges. Physiol. (Berl.)*, 1926, **215**, 273-276.

Through the increase of phagocytic capacity of the exudate leucocytes of a thyroidectomized animal by thyroid implantation or by in vitro addition of Thyreoglandol Roche, thyroid optones, or thyroxine, further support is afforded to Asher's theory of the dependence of phagocytosis on the internal secretions, especially on that of the thyroid.—A. T. C.

A note on tissue respiration in relation to thyroidectomy. Foster (G. L.), *Proc. Soc. Exper. Biol. & Med. (N. Y.)*, 1927, **24**, 334-335.

Rits of diaphragm from thyroidectomized rats showed tissue respiration 25% to 30% below the average normal for unoperated animals.—J. C. D.

Thyroxin and growth of white mice (*Thyroxinversuche an weissen Mäusen*). Glaser (M.), *Ztschr. f. Anat. u. Entwicklungsgesch. (Berl.)*, 1926, **80**, 704-725.

Thyroxin in small doses (.01 mg. daily for 63 days to 16 weeks old mice, as an example of a particular experiment), accelerated growth in body weight. Adipose tissue, suprarenals, spleen and thymus were over-weight. The heart was dilated. Larger doses (starting with .02 mg. and increasing to .08 mg.—an average of slightly more than .04 mg. per day for 22 days to 20-21 weeks old mice) caused a loss of 25% in body weight. Glycosuria and albuminuria of questionable origin were noted. The pancreas gave evidence of endocrine insufficiency.—A. T. R.

Diagnosis of disturbed thyroid function by the interferometric blood test (*Die Artdiagnose thyreogoner Funktionsstörungen mit Hilfe der interferometrischen Blutuntersuchung*). Groedel (F. M.) & Hubert (G.), *Schweiz. med. Wchnschr. (Basel)*, 1926, **56**, 949-950.

This report stresses as proved the specificity of the interferometric blood test in the diagnosis of disturbances of thyroid function and the degree of these disturbances, based upon observations in 10 cases.—I. B.

Effect of pilocarpine on the electrocardiogram in normal, in thyroid treated, and in thyroidectomized guinea pigs and rabbits. Herzfeld (E.) & Mosler (E.), *Arch. f. exper. Path. u. Pharmacol. (Leipz.)*, 1926, **114**, 170-176; *Abst. Chem Absts.*, **21**, 276.

In normal rabbits and guinea pigs pilocarpine usually causes a retardation in the pulse. In guinea pigs which have been fed thyroid and administration of large doses of pilocarpine induce much the same changes as in normal subjects, but with moderate doses the disturbances in conduction are less than in the normal animals. Thyroidectomized rabbits behave as do normal animals.

Tuberculosis of the thyroid gland, with a report of five cases. Higgins (C. C.), *Internat. Clin. (Phila.)*, 1926 (Series 36), 4, 269-275.

Five cases of tuberculosis of the thyroid gland from the service of Dr. G. W. Crile are reported. Nine cases were reported in 1917, making a total of fourteen cases in his series. That tuberculosis of the thyroid gland is of rare occurrence as indicated by the literature as well as by the above small group, which is only 0.15% of the total number of thyroidectomies included in Dr. Crile's total series. The frequent association of hyperthyroidism with tuberculosis of the thyroid gland is indicated by the fact that in 10 of the 14 cases the gland showed increased activity. Because of the fact that in many cases of tuberculosis of the thyroid gland pulmonary tuberculosis is present, regional rather than general anesthesia should be used, and a general hygienic regimen should be instituted to improve the patient's resistance and to further the healing of the pulmonary lesion.—I. B.

Some notes on the iodine compounds of the thyroid. Ingvaldsen (T.) & Cameron (A. T.), *Tr. Roy. Soc. Can. (Ottawa)*, 1926, 20, Sect. V, 297-306.

From its solubility properties iodothyroglobulin should correctly be termed a pseudo-globulin. From it an impure preparation of thyroxine has been obtained containing 38.5% of iodine. When nitrous acid is added to a solution of diiodotyrosine an orange-yellow color is obtained (as contrasted with the lemon-yellow color given by thyroxine). This changes to red on addition of ammonia or sodium hydroxide. The development of the red color is equal for equal molecular concentrations of diiodotyrosine and thyroxine. It seems to be specific for these two compounds, and is not given by dibromotyrosine nor by a large number of other benzene derivatives. After hydrolysis of thyroid tissue by baryta and removal of the thyroxine fraction by acidification, when the remainder is concentrated by various procedures solutions are obtained which still give a marked positive reaction with nitrous acid and ammonia, suggesting that diiodotyrosine is present. It has not been isolated. When diiodotyrosine is added to pancreas tissue to give an iodine concentration comparable with that in thyroid tissue, after hydrolysis only a trace of diiodotyrosine can be recovered.—A. T. C.

Histological and microchemical studies on the lipin content of the human thyroid. Jaffe (R. H.), *Proc. Soc. Exper. Biol. & Med. (N. Y.)*, 1927, **24**, 348-349.

A brief statement of the qualities of lipid granules found in increasing numbers after the first year of life. They are products of the secretory activity of the epithelial cells of the thyroid.—J. C. D.

Diabetes mellitus and myxoedema. Jamieson (H. C.), *Canad. M. Ass. J. (Montreal)*, 1927, **17**, 88-89.

A male, 37 years of age, showed classical symptoms of myxoedema, with a possibly much earlier history of diabetes, which was not now evident. Administration of thyroid produced the classical symptoms of diabetes. These ceased with cessation of this treatment and regression to myxoedema. He was balanced with thyroid and small doses of insulin.—A. T. C.

Goitre—from the standpoint of prevention. Keith (W. D.), *Canad. M. Ass. J. (Montreal)*, 1926, **16**, 1171-1175.

In British Columbia it is found that there is relatively a greatly increased incidence of goitre where the drinking water is turbid and murky in character. Keith considers that since this water frequently contains some iodine, there must be something present influencing the occurrence of goitre, perhaps through the conversion of iodine into an unassimilable form. Incidence of goitre and amount of iodine in the drinking water have been compared for a number of districts. The Pemberton valley, where previous to the anaphylactic use of iodide the incidence of goitre was over 80%, has (river) drinking water containing 103 parts of iodine per million. The water is very turbid, with a heavy sediment. The clear drinking water of Vancouver contains no detectable iodine, but the incidence of goitre there is only 8%.—A. T. C.

The physiological background for the symptoms of thyroid failure, with a consideration of the results of treatment. Lawrence (C. H.), *Boston M. & S. J.*, 1927, **196**, 43-48.

The results of a careful study of 40 cases are tabulated. The author concludes: "That the presence of myxedema, certainly as determined by inspection, is not essential to the existence of marked thyroid failure. There is considerable evidence that its presence is fully as dependent on vascular pathology as on diminished thyroid function per se. Abnormal fatigability of the body as a whole, or subnormal function of any of its parts, should, in default of demonstrable organic disease, suggest depression of thyroid activity. The presence of such a depression can be determined, in the majority of patients, only by careful tests of vital function of which the basal

metabolism is only one, and the administration of thyroid extract is not often justifiable without the evidences afforded by such tests. Thyroid failure produces symptoms through its specific effects on bodily nutrition, and may be expected to benefit symptoms only in so far as it can normalize the nutritional level of the body."—J. C. D.

Diagnosis and classification of attenuated forms of hypothyroidism (*Diagnóstico y clasificación de las formas atenuadas de hipotiroidismo*). Marañón (G.), *Arch. d. Endocrinol. y Nutrición* (Madrid), 1925, 6, 400-414.

The three phases of hypothyroidism are divided into three groups: Cases with a complete clinical syndrome of myxedema; cases with symptoms of insufficient thyroid, but with the general form of myxedema; cases in which the hypothyroidism shows a union of other pathologic conditions of distinct etiology, but whose appearances are determined by the hypothyroidism. In the second group Marañón has isolated various clinical forms; edematous, adipose, circulatory, genital and hemorrhagic. In the last group are found the affections which are sometimes not originated directly from deficient thyroid, but which show a terrain predisposed by this deficiency and which improve with thyroid treatment. Examples are: some cases of chronic rheumatism, certain dermatoses (eczemas, psoriasis, acne, etc.); sometimes chronic infections and relapses; pharyngitis (Leopold-Levi and Rothschild); recurrent appendicitis (Torre and Marañón); erysipelas (Leopold-Levi and Rothschild, Bonilla, etc.).—E. B.

Thyroid alterations in hereditary syphilis (*Contributo alla conoscenza delle alterazioni della tiroide nella sifilide ereditaria*). Morelli (Elisa), *Boll. dell. Ist. Sieroter.* (Milano), 1925, 4, 215-223.

A histological study was made in seven cases. It was found that in early hereditary syphilis there are hyperplasia and anomalies in the connective elements, altered architecture of the organ, epithelial degeneration and formation of abnormal colloidal substance. In the late form the organ is less compromised, but it is in instable equilibrium since it responds excessively to the stimulations. In both cases with tissue degeneration there are some manifestations of vicarious hyperplasia.—P. M. N.

Experimental researches on goiter-cretinism (*Ricerche sperimentali sulla tiroide—In relazione alla etiologia del Gozzo-cretinismo*). Pighini (G.), *Riv. Sperimentale di Freniatria* (Reggio-Emilia, Italy), 1926, 1, Pp. 93.

Pighini adheres to the hydric theory of endemic goiter. He administered toxic substances to different animals and noted the effects on the thyroid. It was found that many substances may de-

termine alterations in the gland: that there is no specific alteration due to a special substance, but that such alterations are determined by the intensity of action of the toxic principle and by the constitution of the subject. With extensive intoxication there occurred acute degeneration of the cells with loss of colloid and degeneration of the vessels leading to atrophy of the parenchyma. With milder intoxication hyperplasia of the parenchyma followed gradually by the phase of colloid adenoma was noted; in the parenchymatous as well as in the adenomatous forms the gland showed deficiency of iodine in the colloid. With the alterations of the thyroid there was found alteration of the thymus, adrenals and, in severe cases, of the sexual glands and the hypophysis. The several types of experimental strumas were very much alike even though in different animals, and very striking was their likeness to the types of human goiters. The experiments prove that lack of iodine is not the cause of endemic goiter. The author denies the "often asserted" compensative hypertrophy of the gland. He postulates a toxic substance acting on the organism and especially on the thyroid, entering in combination with the iodine in the organism—and especially in the thyroid—and determining chemical modifications, owing to which its biologic properties are lost. There are many substances either from outside or from the organism apt to enter in such a combination with the iodine compounds of the thyroid, hence causes of goiter are very likely more than one. They probably are to be found in the water of the regions of endemic goiter, and their amount probably does not need to be great to have its effect. The author cannot specifically incriminate any of the substances employed in his experiments as the real cause of goiter.—G. Vercellini.

I. Production of mydriasis in white rabbits by the injection of thyro-toxic blood serum and adrenaline; II. Detection of a toxic principle in the blood. Pitfield (R. L.), *Med. J. & Rec. (N. Y.)*, 1926, **123**, 752-754.

The investigator is impressed with the fact that a toxic substance circulates in the blood of patients ill of hyperthyroidism. The reaction which he devised consists in the injection of 1 cc. of serum, freshly drawn, into a white rabbit (female preferred). In 2 minutes adrenaline (1-1.000) is instilled into one eye every four minutes (2 drops at a time). If the blood is toxic a complete mydriasis will appear after 1 cc. of adrenaline solution has been used. There must not be more than 1 cc. of serum used. Often a much less amount will produce the reaction. The mydriasis must be so complete that no portion of the iris of the treated eye shall respond to the influence of a very bright electric light held close to the cornea. Instillations of adrenaline of this dilution will not produce mydriasis alone nor will the injection of serum alone do this.

Serum heated to the point of distillation (100° C.) does not destroy the toxic principle for the distillate if injected into a rabbit (2 cc.) and adrenaline applied to the cornea, still causes a reaction. Some of the same serum from the patient which produced a prompt reaction when exposed to the influence of light and air lost this property after an exposure of 72 hours. It is presumed by this investigator that the hypothetical substance was destroyed by the oxygen and light. The reaction generally appeared in toxic cases in from 28 to 35 minutes. It is not considered positive if the reaction does not appear in 60 minutes. The more toxic cases reacted much more promptly than did the less toxic. In general the metabolic rate ran parallel to the intensity of the reaction. The more toxic the case, the longer mydriasis will persist. One case was so intense that it persisted for 12 hours.—Author's abstract.

Studies on the Arneth count III. The effect of thyroidectomy.

Ponder (E.) & Flint (K. N.), Quar. J. Exper. Physiol. (Lond.), 1926, 16, 225.

Although it has been shown that thyroid injections alter the Arneth count in that there is an increase in polymorphonuclear cells with simpler formed nuclei, the removal of the thyroid in rabbits does not affect the count. These results are interpreted as meaning that thyroid injection increases the activity of the bone marrow, but that removal of thyroid influence does not alter the stage of maturity at which these cells are liberated.—C. I. R.

Studies on the Arneth count. IV. The deflection of the count by thyroid injections. Ponder (E.), Quar. J. Exper. Physiol. (Lond.), 1926, 16, 227.

Thyroid injections in rabbits were followed by a pronounced relative and absolute increase in cells of Class I. Leucocytosis persisted for three days after which there was a steady decline until the count returned to normal in 2-3 weeks. With progressive decline in the number of cells in Class I there was an increase in Class II, which reached a maximum about the third day. Class III reached a maximum about the sixth day, Class IV about the eleventh day, and Class V just before leucocytosis disappeared, the increase in each class being progressively less than in the preceding class. This regression is interpreted to mean that thyroid induces the entrance into the blood stream of many young cells as Class I, which pass through successive classes and finally leave the circulation chiefly as Class IV and Class V cells. The author calculates that 10,000,000 polymorphs are produced per day by the bone marrow.—C. I. R.

Thyroidectomy: Its relation to cure of thyrotoxicosis. Richter (H. M.), J. Am. M. Ass. (Chicago), 1927, 88, 888-892; Abst. A. M. A.

Richter says that aside from all question of the exciting cause, the immediate source of the clinical syndrome called exophthalmic goiter lies entirely within the thyroid gland. Tomorrow we may be able to reach the activating agent; today we must reach the activated gland itself. Its removal is incompatible with the continued existence of the disease in its various forms. In his own work, cases are not selected. He operates on every patient with toxic goiter, either exophthalmic or adenomatous, who consents. The only exceptions have been those who have died within a few hours of admission. Patients are not sent away to "recuperate" for operation, nor is a patient held too ill for operation; preliminary preparation usually ranges from ten to twenty days. Cardiac decompensation and fibrillation may cause some delay; Richter insists that fibrillation, particularly, must not be considered a contraindication for surgery. Nothing is to be hoped for in such cases in the presence of continuous thyrotoxicosis; nothing in surgery is more brilliant than the recovery after adequate thyroidectomy. As a basis for these statements Richter offers an analysis of the results obtained with 100 recent consecutive patients, who were operated on by himself and two colleagues. Approximately 93% were free from any evidence of thyrotoxicosis. Seven per cent had either a recurrence of some degree of intoxication or some degree of hypothyroidism. A study of the condition of the 93% that were free from any evidence of toxic symptoms showed that of those who were operated on in the early stages of their disease practically none had any evidence of permanent secondary pathologic change, whereas of those who were operated on after a long period of intoxication, the proportion showing permanent secondary pathologic change, mainly cardiac, was remarkably high, more than 50%. Though these patients showed more or less marked secondary pathologic changes, all were entirely free of thyrotoxicosis. There were seventy-six primary hyperplastic goiters and twenty-four secondarily toxic (adenomatous) goiters. The average basal metabolic rate before therapy, other than rest, diet and sedatives, for a few days was 50.5 plus. All were placed on preliminary iodine therapy in the form of compound solution of iodine, the dosage usually ranging from 30 to 40 minims (2 to 2.5 cc.) daily. Some patients had been excessively overdosed with iodine before entering. In unusually severe cases, much larger doses were given. The first postoperative metabolism studies were begun before the patient was discharged from the hospital in most cases, but in many they could not be made until after their return home. Ninety-four of the 100 patients showed an immediate fall of the basal metabolic rate below plus 15. The average rate of these ninety-four patients was plus 1.6. Of six who had a

persistently raised postoperative rate, four averaged 40 plus. These patients have been reoperated on, and in each case a mass of thyroid tissue was found and removed. The metabolism rates fell to normal in all, averaging 5.9. One patient has a persistently high metabolism averaging 40 plus. One patient has a metabolism of 28 plus eleven months after operation. Of the six patients in whom the immediate results were poor, all were so greatly improved that on the basis of their own estimation of their condition they might have been reported as cured. The patient with a persistent metabolism of 40 plus refuses operation because of her subjective feeling of well being. Of the 100 patients operated on, ninety-eight are completely restored, four after reoperation, and two require reoperation. The total patient mortality for the last three years has been 1.52%.

Myxedema and exophthalmic goiter. Richter (W.), Dermat. Wchnschr. (Leipz.), 1927, 84, 51; Abst., J. Am. M. Ass., 88, 969.

Richter reviews the literature on myxedema and on skin changes seen in exophthalmic goiter. In a personal case, myxedema of the legs, histologically typical, developed in a man, aged 25, about five years after the first appearance of a swelling in the neck and about two years after partial strumectomy for exophthalmic goiter. When Richter saw the patient there was a cushion-like swelling of the skin on the anterior surface of both legs, from the upper third of the leg to the ankle. This condition had had its onset one year before. Heart, blood picture and coagulation time and basal metabolism were normal, but the subjective symptoms had become severe. A second operation was performed on the thyroid, to which the patient succumbed. The results of the histologic examination of the thyroid tissue were atypical for exophthalmic goiter; areas of regeneration adjoined areas where the structure was distinctly that of exophthalmic goiter. Richter believes that we have here the rarely observed hypothyroid stage of exophthalmic goiter and that the skin changes point to hypothyreosis as the accompanying hormonal disturbance of that stage. This offers an explanation of the puzzling association of myxedema and exophthalmic goiter.

Changes in the growth of skeletal muscle following thyroidectomy in the sheep. Simpson (Ethel D.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1927, 24, 289.

Normal development of the cytoplasm is prevented after early thyroidectomy. The muscle cell shows all the normal element, but in the proportion seen normally only in very young animals.

—J. C. D.

Endocrinology

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STUDIES ON VIGOR XVI. ENDOCRINE FACTORS IN VIGOR*†

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During the past three years various members of the Physiology Department of the Ohio State University have been engaged in a series of investigations on the various factors that serve to modify the vigor of the individual. The method (1) is to confine albino rats in small housing cages having uninterrupted access to revolving cylinders in which they can exercise *ad libitum*. The revolutions are automatically recorded by ratchet counters. Observations upon hundreds of individuals have shown that so large a part of the total energy expenditure goes to running in the wheels that a record of the revolutions of these serves as a rather accurate criterion of the animal's tendency to exercise, hence, presumably, of its general vigor.

The activity of rats thus determined is notably variable, both as regards the individual and as regards large groups. It was

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assumed in the beginning that if a sufficient number of individual determinations was made the record of total colony revolutions per day would be fairly constant. Such, however, is not the case. On some days most of the animals are relatively active, and on other days some degree of depression is seen. Attempts have been made to correlate these differences with a variety of meteorological factors, such as temperature, barometric pressure, wind velocity and direction, luminosity, humidity, and diurnal variations of temperature. No simple relationship has been discovered. The methods of partial correlation, however, have not been adequately applied.

Another finding that was not anticipated, considering the uniformity of heredity and environment, is that there is marked variation in the spontaneous activity of litter-mates, even though all are apparently equally healthy and alert. In a few cases autopsy studies have been made of the endocrine gland weights of high and of low activity animals. There is a suggestion that high activity may be correlated with large thyroids, sex glands and adrenals, but the data so far secured are not consistent nor adequate.

THE PINEAL

No successful studies have as yet been made on the pineal gland.

THE HYPOPHYSIS

A few clinical observations have given the impression that "pituitrin" is of some benefit in cases of asthenia in the human subject. To a few rats showing low activity this extract was administered subcutaneously in 0.1 or 0.2 cc. doses, daily. No improvement in activity was seen. No other experiments directly involving the hypophysis have been made.

THE THYROID

It was confidently expected, in view of its well-known effect on basal metabolism that thyroid deficiency would materially reduce the spontaneous activity. This operation, however, in some 25 rats, has had little or no effect. Careful autopsies indicate that the tissue of the thyroid gland, proper, in nearly all cases had been completely removed. Whether undiscovered bits of

thyroid tissue were left behind in sufficient amount to maintain an adequate supply of secretion or whether compensation occurred in other glands has not been determined. The details on 20 of these animals will be reported by Van Buskirk and Lee.

That thyroid extract has a general "tonic" effect has been claimed by some clinicians and denied by others. As a test of the theory, desiccated thyroid gland substance was administered to 11 senile animals in dosage of 0.1 grain three times a week to 1 grain six times a week. The effects were either negative or depressant. Similar experiments in castrated animals showing marked deficiency in spontaneous activity gave, likewise, negative results. In two cases thyroid substance was administered to rats from which the thyroids and parathyroids had been removed. In view of the negative result from thyroidectomy, it is not surprising that no increased activity was seen. Whether as coincidence, or otherwise, these two thyroidectomized animals seemed especially susceptible to the toxic influence of the drug and showed a marked decrease in activity.

THE PARATHYROIDS

Results of parathyroidectomy in the animals that survived operation have been consistently negative so far as spontaneous activity is concerned.

THE ADRENALS

Since the old experiments of Phillippeau and of Hartley it has been widely assumed that adrenal extirpation has no influence on the vital processes of the rat. This anomaly has been explained on the grounds that the animal is rather abundantly supplied with accessory adrenal tissue. It is true that after ablation of both glands the rat seems normally alert and active. Durrant (2) has shown, however, that in a considerable proportion of cases the rats, when placed in recording cages, show a marked degree of chronic adynamia. In the animals that recover normal activity, hypertrophied cortical rests near the site of the glands, proper, were ordinarily found.

Gans and Miley (3) have made ergographic studies on 22 rats from which both adrenals had been removed within a period of 1 to 8 days, as well as on control animals. It was found that, although the absolute strength of the gastrocnemius mus-

cles was essentially the same in both groups, the rats lacking adrenals showed much greater fatigability and were capable of giving, on the average only 1/16 as much work as were their controls before complete fatigue set in.

Rats showing chronic adynamia after adrenal extirpation would seem to be particularly favorable subjects for studies on experimental therapeutics. A somewhat extensive series of such studies was made by Durrant and the writer. In brief, it was found that glycerine extracts of whole adrenal gland could not be administered hypodermically without causing serious ulceration and marked impairment of activity. No improvement of activity was seen with smaller doses given by mouth, and larger doses killed the animals. Surmising that the deleterious effects might be due to the contained adrenalin, the experiments were repeated with glycerine extract of cortex, only, fed by mouth. In no case, however, was any convincing evidence obtained that such extracts are of benefit.*

THE PANCREAS

No experiments have been made either by extirpation or by administering insulin.

THE OVARIES

The observations of Wang (4) that extirpation of the ovaries markedly reduces the spontaneous activity of the rat was readily confirmed. How the reduction is brought about, however, offers a somewhat difficult problem. An approach to its solution has been made by Miley (5), who studied the incidence of fatigue in the gastrocnemius muscles of normal and of spayed rats stimulated in situ by faradizing the sciatic nerves. It was found that the absolute strength of the muscles, gram for gram, was 40 per cent greater in the control than in the experimental animals, and the total amount of work elicitable before complete fatigue was only 33.6 per cent as great in the spayed rats as in the controls. These results obviously carry the problem only one stage further. Whether the adynamia is due to interference with the metabolism of the muscle or its innervation, or to failure of supporting bodily functions, such as respiration, circulation, sugar supply, or what not, remains to be determined.

* We are indebted to Armour & Co., Chicago, and to Mr. Frederick Fenger of this firm for generous supplies of material.

Attempts to restore the vigor of spayed animals by the administration of ovarian products have been so far without success, although Wang has shown that this can be accomplished handily by means of ovarian grafts. In view of the claims of Hancher and Rogers that marked improvement was obtained in clinical cases from the oral administration of glycerine extracts of ovary, it was hoped that such would prove efficacious under exactly controlled experimental conditions (revolving cage method). In the hands of Durrant (1) the method gave completely negative results.

Similarly negative results were obtained from subcutaneous injections of aqueous extracts of corpus luteum, using Hynson, Westcott and Dunning and Eli Lilly commercial products (Durrant, 6). That the corpus luteum extracts were not entirely inert, however, is indicated by the fact that animals to which they were administered showed considerable loss of fertility.

In view of the fact that the energizing effect of the ovary is presumably due to hormone factors and of the claims by certain clinicians that hysterectomy causes ovarian depression, Durrant (7) investigated the effect of this operation on vigor. The results in this case, also, were negative.

THE TESTES AND PROSTATE

That castration results in some degree of loss of aggressiveness has long been recognized. In accordance with this fact it was found that castrated rats kept in the recording cages showed a marked reduction in spontaneous activity (8). When the operation was performed at the early adult period the activity was cut down five fold. When, however, the operation was performed within the first 12 days of life, Gans (9) showed in 25 rats that no reduction in activity was brought about. No evidence has been secured as to what sort of compensating changes take place to prevent the loss of vigor under these conditions. The same investigator (10) has secured data on 10 animals to indicate that loss of one testis is without effect, but that with only a half testis left in situ the activity is cut down some 25 per cent. Removal of still larger proportions of the testis tissue results in still greater decrements of activity. This series should be further extended.

Gans and Hoskins (11) made ergographic studies on 15 castrated rats showing marked degrees of loss of spontaneous activity. It was found that, although the absolute strength of the *gastrocnemii* was as great in the castrates as the controls, fatigue supervened more quickly and the total work elicitable under repeated stimulations was only 64 per cent of that of the controls. The underlying cause of the increased fatigability has not been determined.

We have had many opportunities to confirm Slonaker's observation that senile rats show greatly decreased activity. To what extent the loss of sex hormones accounts for this lethargy is not known.

During the past two years many attempts have been made to restore the vigor of castrated and senile animals by *testis* grafts. One series of studies giving completely negative results has already been reported. A repetition of the grafting experiments was carried out in some 40 other animals. Here, again, negative results were secured in all castrates and all but two senile animals. In these two, single grafts of testes from rats 10-12 days old affixed directly to the testes of the hosts was followed by a consistent though not extensive increase in activity that persisted three or four months.

In practically all cases studied in our completed series, entire resorption of the grafts has taken place. Since other observers have reported frequent "takes" in the rat, and since our own technic has been carefully carried out, we have been led to suspect that the activity in the recording wheels may have prevented any significant persistence of the grafts.

Smith (13) has recently shown in case of the hypophysis that, although single grafts are without perceptible influence, daily repetition of the grafting leads to marked physiological effects. In collaboration with Boukalik another series of experiments is being carried out on castrates and senile animals. The *testis* material has been secured from rats about 120 grams in weight and implanted by the Stanley syringe method in various loci—under the skin along the ventral wall and in the scrotum. At first 0.1 to 0.2 cc. was implanted three times, then six times a week. In two instances some apparently significant increase in activity was seen within a few days. The experiments are being continued with larger amounts of gland substance.

In collaboration with J. B. Brown and Milton O. Lee an extensive series of experiments (not hitherto reported) was carried out on the effects of feeding desiccated testis and of subcutaneous injections of a variety of testis extracts. These latter included saline, glycerine and lipoid-solvent extracts (Allen and Doisy method) and dialysates of various sorts (distilled water, saline, weak acid and alcohol). Without going into laborious detail, suffice it to say that no significant increase on activity was seen in any case.

Lee has made similar experiments with a saline extract of prostate gland supplied by the Eli Lilly Co. The results in this series, also, were negative.

The possibility has occurred to us, and has been suggested by various investigators with whom the work has been discussed, that simultaneous administration of prostatic and testis extracts might give better results. Opportunity has not been had, as yet, to test the possibility.

Vasectomy in senile animals has consistently failed to give any improvement in apparent vigor.

Whether the ovaries or the testes afford a more potent energizing hormone offers an interesting question. Since both sexes are reduced to a similar state of lethargy by removing the primary sex glands, and since the normal female shows about twice the activity of the male (Hitchcock, 15) it would seem that the palm goes to the ovary.

CORRELATION OF VOLUNTARY ACTIVITY AND BASAL METABOLISM

Dr. Milton O. Lee, who has given special attention to this topic, has supplied me with the following notes. It might be supposed that there is a causal relationship between the basal metabolic level in an animal and the amount of voluntary activity which it shows. Data from a number of sources give some information on this point.

1. *The effect of thyroidectomy.* Removal of the thyroid glands, which are primary regulators of metabolism, has been shown to have no effect whatever upon the voluntary activity of rats. In a series of 20 experimental and 20 control animals the average daily activity was almost exactly the same in each group.

2. *The oestrous cycle.* If there exists any correlation be-

tween the general metabolic level and the amount of voluntary activity, one would expect to find an increased basal metabolic rate during those stages of the oestrous cycle characterized by increased activity. In stage II of the cycle, for example, the voluntary activity is increased 200 to 400 per cent over the level in the other stages. At this time, however, there is no significant change in the basal metabolic rate. At least 50 determinations of basal metabolism during the oestrous stage in 10 different rats failed to show any constant increase or decrease as compared with the average level throughout the cycle.

Furthermore, there is an increase in the basal metabolic rate during the last few hours of the rest interval or Stage V of the cycle, when, however, there is no marked change in the voluntary activity. During the whole of Stage V of the cycle this activity is comparatively low.

3. *The effect of spaying.* Spaying has been shown to have a remarkable effect upon the voluntary activity, resulting in a decrease of 60 per cent or more. This decrease is not closely correlated with any decrease in the basal metabolic level. Determinations on five spayed rats over a period of three months have shown a decrease in basal metabolic rate of only about 10 per cent.

4. *Effect of ovarian hormone injection.* In two cases the basal metabolic rate was not changed upon the injection of ovarian hormone into spayed rats, even though rather typical oestral cycles resulted.

In view of these facts, it seems possible to conclude definitely that there is no relation between the basal metabolic level and the amount of voluntary activity which the animal shows.

SUMMARY

In summary it may be said that determinations of spontaneous activity in rats kept in recording cages have disclosed no effects from thyroid or parathyroid extirpation or thyroid feeding. Adrenal extirpation often induces adynamia of from two weeks to permanent duration. Ergographic studies show reduction of work capacity of individual muscles to 1/16 normal. Glycerine extracts of adrenal gland (whole or cortex, only) by mouth or subcutaneously had no beneficial influence on voluntary

activity. Females are spontaneously more active than males, hence the ovarian hormone is presumably more potent than that of the testis. Castration and spaying results in marked decrease of spontaneous activity and of work capacity of individual muscles. Hysterectomy had no demonstrable influence. As shown by Wang activity can be restored approximately to normal by ovarian grafts. In our laboratory oral administration of glycerine extract of whole ovary, subcutaneous injection of saline extract of corpus luteum, saline prostatic extract and numerous sorts of testicular extracts, as well as testis feeding and vasectomy, have had no invigorating effect. Testis grafts have given almost but not quite completely negative results. No constant correlation between changes of basal metabolism and voluntary activity has been discovered.

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PSYCHIC TRAUMA IN PATHOGENESIS OF EXOPHTHALMIC GOITER*

A Review of 3343 Cases

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The taking of a careful history in patients with exophthalmic goiter commonly yields three important facts: (1) Information to the effect that one or more blood relatives is or had been suffering with "nervousness," exophthalmic goiter, or diabetes mellitus; (2) the patient has been of more or less "nervous" temperament, characterized by irritability, impatience, fractiousness, and emotionalism, usually since childhood; (3) the onset of the symptoms of the disease followed soon after the occurrence of a psychic trauma.

From the frequency with which such histories are elicited, it appears that there is a strong congenital predisposition to the disease. Indeed, in quite a series of the cases herein reported, two, three, and even four members of a family have been afflicted with exophthalmic goiter. In the absence of an exciting cause, such a predisposition may not be recognizable nor tangibly mar the individual's physical and mental well-being throughout a normal span of existence. There are doubtless many thousands of individuals possessing a strong susceptibility to exophthalmic goiter who are going through life in an apparently normal manner, oblivious to possibilities which would likely follow the incidence of a psychic trauma.

The term psychic trauma applies itself to all conditions in which, with or without physical injury, the mind has received an impact or shock from which it does not readily recover to its former standard. The subconsciousness is especially involved. The shock may result from a cause acutely, subacutely, or chronically operative. The instinct of fear is the basis of

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psychic trauma and is unduly prominent in individuals susceptible to exophthalmic goiter.

PREDISPOSING "SOIL" IN TEMPERAMENT

As pointed out elsewhere,¹ we might state that the earmarks of susceptibility to exophthalmic goiter are: (a) heightened cerebration in which the mental alertness of the individual is above the average; (b) emotional instability; (c) excitable heart with labile pulse; (d) vasomotor ataxia characterized by dermatographia, a tendency toward undue sweating, and undue surface heat; (e) sparkling eyes which during conversation and active attention may lead to a suspicion of exophthalmos; and (f) an unduly palpable thyroid gland which may, strictly speaking, still be within normal limits in size. These persons are to be found everywhere, more especially among Caucasians whose mentality is at the highest state of development. Psychologically, one might say that the chief characteristic of this class of individuals is an abnormally lowered threshold of emotional reaction.

EXCITING CAUSES OF EXOPHTHALMIC GOITER AS ELICITED IN 3343 PATIENTS OBSERVED IN 15 YEARS (JANUARY, 1911, TO JANUARY, 1926)

PSYCHIC TRAUMATA				General Infections (Influenza, Pneumonia, Syphilis, Etc.)	Focal Infections (in Teeth, Tonsils, Etc.)	Iodine Ingestion	Thyroid Extract Ingestion	No Stated Exciting Cause
Accident or Imminent Personal Danger	Minor Surgery (Ton- sillectomy, Curetage, Etc.)	Partur- ition	Worry, Grief, Disap- pointment, Sexual Incom- patibility, Etc. (d)					
(a)	(b)	(c)	(d)					
435 (13%)	234 (7%)	134 (4%)	2039 (61%)	100 (3%)	67 (2%)	100 (3%)	33 (1%)	201 (6%)

THE COMMON EXCITING CAUSE

The individual above described is singled out of the crowd to become the subject of exophthalmic goiter in a situation in which the instinct of self-preservation is called upon to decide between fight or flight. On the firing line in battle, during a conflagration, an earthquake, a shipwreck, or a train accident,

forty-nine out of fifty persons may emerge from the harrowing experience, quickly to recoil to usual physical and mental health. One of them, however, quickly or gradually develops symptoms merging into the typical picture of "frozen fright" characterizing exophthalmic goiter. The eyes stare, the heart palpitates, there is subjective and objective trembling, the skin is constantly moist, insomnia becomes complete, emotionalism dominates the mental existence, there is rapid loss in weight, and the basal metabolism rises beyond all bounds. This form of psychic trauma (accidents or imminent personal danger) was elicited in the histories of 435 patients, or 13 per cent. of this series. The following are typical examples:

1. Miss E. K., age 15, was in an automobile accident.
2. Mr. N. E., age 40, was struck by a trolley car.
3. Mrs. E. T., age 52, fell down a flight of stairs.
4. Mrs. M. P., age 26, was frightened by a fire next door. The following day the police raided her home by mistake.
5. Mrs. E. M., age 22, fell under a wagon.
6. Mr. E. K., age 32, while serving as government inspector in a munitions factory during the World War, saw a freight train jump the track and land into a warehouse filled with shells.
7. Mr. S. C., age 29, was made extremely nervous over the possibility of being sent to the front in the World War, though he had not yet been sent across the Atlantic.
8. Mr. J. O., age 32, drove his automobile in front of a train and made a very narrow escape.
9. Mrs. H. B., age 26, was very badly frightened by being informed that she was suffering with tuberculosis; shortly thereafter she participated in an automobile accident.
10. Mr. C. S., age 24, met with an accident in which he sustained the loss of an eye.
11. Mrs. E. G., age 31, was caught in a subway fire.
12. Dr. H. B., age 31, struck his head very forcibly against a steel beam.
13. Miss H. K., age 23, had a narrow escape from drowning.
14. Mr. S. A., age 32, had a narrow escape in a severe automobile accident.
15. Mr. L. B., age 32, was struck in the face by a golf ball.

Another form of acute psychic trauma may be described as resulting from the mental shock incident to surgical operations, usually minor, as tonsillectomy, nasal operations, uterine curetage, and the like. The number of patients presenting a history of the disease following minor surgery is 234, or 7 per cent. of the series. A patient may assume an air of bravado immediately before tonsils are removed, and yet become so badly frightened during the first few steps of the operation as to be shocked into the development of Graves' syndrome. This is no

argument against tonsillectomy in general. Since exophthalmic goiter following the shock of tonsillectomy almost invariably occurs in those operated upon under local anesthesia, it is suggested that the candidate for tonsillectomy be studied pre-operatively with a view to determining whether it would not be best to administer a general rather than a local anesthetic. The following are typical examples of this form of psychic trauma:

1. Mrs. A. O., age 24, had tonsillectomy performed two months before onset of symptoms.
2. Mrs. L. C., age 26, had tonsillectomy performed which was immediately followed by a "nervous breakdown" culminating in exophthalmic goiter.
3. Miss S. G., age 24, presents a similar history.
4. Mrs. M. S., age 26, stated that tonsillectomy was followed in three months by outspoken evidences of exophthalmic goiter.
5. Dr. E. R., age 42, presents a similar history.
6. Mr. M. M., age 28, had appendectomy performed. Patient states that it was not the operation but the ether that frightened him into the development of exophthalmic goiter.
7. Mrs. C. F., age 28, had a curetage without a general anesthetic.
8. Mr. R. MacD., age 43, stated that symptoms of exophthalmic goiter followed several days after the extraction of several molar teeth under local anesthesia.

Parturition, being associated with apprehension for self and offspring, as well as the ordeal of labor pains, is more likely to be the exciting cause of exophthalmic goiter than pregnancy itself, and constitutes an obvious psychic trauma. In this series, 134 patients (4 per cent.) developed exophthalmic goiter very shortly after delivery.

By far the greatest percentage of exciting causes was of a subacute nature, occurring under worry, grief, disappointment, and the like. Such a history was elicited from 2,039 patients, or 61 per cent. of this series. The following are typical examples:

1. Mrs. A. C., age 52, stated that her mother died of cancer. Immediately afterward she became obsessed with the thought that she, too, would die of cancer. Symptoms of exophthalmic goiter developed shortly after her mother's demise.
2. Mrs. E. L., age 53, claimed that symptoms developed as the result of financial worries and marital incompatibility.
3. Mrs. E. G., age 38, stated that the disease developed as a culmination of worriment over her daughter's unhappy marriage.
4. Mr. S. K., age 37, had severe financial strain during the past two years.
5. Mrs. E. K., age 48, had incessant worry over death of children.
6. Mr. S. G., age 30, experienced the shock of two deaths in the family.

7. Mr. H. H., age 37, had to carry a corpse down stairs; a few days later his brother died of influenza.
8. Mrs. J. K., age 20, was badly frightened when her baby fell off her bed.
9. Mrs. F. L., age 47, was "worried to death" over her child who had a double mastoid operation.
10. Mrs. H. S., age 48, received news of the sudden death of her mother and sister in Europe.
11. Mrs. I. S., age 24, suffered from shock because her child fell out of the second-story window and has since been suffering with convulsions.
12. Mrs. A. L., age 28, saw a horse run on pavement and jump over her child. Though the child was unhurt, the mother became hysterical and in a few days developed symptoms of exophthalmic goiter.
13. Miss R. B., age 25, witnessed the gasoline tank of an automobile and the occupant of the car on fire.
14. Mrs. S. G., age 30, saw her child develop convulsions.
15. Miss E. D., age 22, traced her illness to the time when her brother committed suicide.
16. Mr. S. B., age 41, stated that just prior to the onset of symptoms he had a nightmare in which a man with an axe was standing over his mother's bed and was about to decapitate her.
17. Mrs. A. B., age 43, saw her sister's baby burn to death.
18. Mrs. P. A., age 35, had a child who developed infantile paralysis.
19. Mrs. B. R., age 30, went to see a relative in an insane asylum, and on her way out of the institution her pathway was blocked by a lunatic.
20. Mrs. S. S., age 45, suffered from shock due to the death of both parents, which events were closely followed by a fatal accident to her brother-in-law.
21. Mrs. C. McA., age 38, was badly frightened by a negro breaking into her house to rob her.
22. Miss M. M., age 21, had a disappointment in a love affair.
23. Mrs. C. B. attributed her illness to the shock of the accidental poisoning of her child.
24. Mrs. B. T., age 25, was badly frightened by a man. She refused to give details.
25. Mrs. J. W., age 30, was suddenly awakened from sleep to be told that her next-door neighbor had died.

COMMENTS

Exophthalmic goiter appears to be increasing in all civilized countries. The high tension mode of existence during the past decade, with the multiplicity of automobiles, aircraft, highwaymen, "jazz" music, "jazz" thinking and acting, the craving to be entertained, the character of movie and stage presentations, marital incompatibilities and divorces,—all these and many more current factors activate to undermine the neuro-endocrine structures of susceptible individuals to the extent of increasing the incidence of the disease.

The time when the disease asserts itself following the occurrence of the psychic trauma varies with the intensity of the

trauma and the susceptibility of the individual. In quite a few instances of this series the symptoms of the disease presented themselves without any discernible interval of time between cause and effect. In most cases, however, several days or weeks elapsed before the patient became actively aware of the symptoms.

The degree of resistance manifested against the development of exophthalmic goiter may vary in the same person at different times. Also, an individual may be quite resistant to one form of psychic trauma, as, for instance, the shock of an automobile accident, yet become profoundly shocked by business reverses or by the sudden illness or death of a relative. The disease is instigated by an almost hair-spring mechanism and the zone of defense against exophthalmic goiter is so deficient in some individuals that a mere lover's quarrel may instigate the syndrome.

In approximately 15 per cent. of this series there occurred more than one psychic trauma to account for the syndrome. The first seemed merely to weaken the usual defense. Following the second or the third shock, the remaining resistance was broken down and exophthalmic goiter appeared in all its tragic picture.

In the female the psycho-sexual makeup plays a greater rôle in the pathogenesis of the disease than it does in the male. This is easily explained by the fact that the woman's life is largely dominated by her sexual existence, both from the standpoint of maternal instinct and from the fact that her sexual mechanism is much more complicated. Since sexual maladaptation is common, this form of psychic trauma is frequently encountered as the exciting cause of exophthalmic goiter.

Occupational, environmental and economical maladaptation and discontent are likewise forms of psychic trauma if continuous with no possibility of adjustment in view. This thwarting of happiness, apparently hopeless, may so prey on the mind of the individual as to constitute the exciting cause of the disease.

In probably 40 per cent of case histories the patient claims to have had a "nervous breakdown" weeks, months and occasionally a year or two preceding the onset of the existing syndrome. The "breakdown" is usually preceded by some emotional or nervous tension of acute or chronic nature, and is not followed by complete recovery. Some of the symptoms such as sensations

of trembling, apprehension, palpitation, restless sleep, and undernourishment still persist, although the individual as a rule is capable of resuming some or all of the customary duties. A relapse of the "breakdown" soon follows, which culminates in the syndrome of exophthalmic goiter.

While the patient is progressing toward recovery and still requires observation and the symptomatology is on the wane but has not yet disappeared, the resisting forces are as yet incapable of defending the individual against relapse. The patient is unsafe in an automobile accident, shipwreck or conflagration, or even in a family quarrel. An added shock in an improved patient may result in a symptomatology far more severe than that presented by the primary attack of exophthalmic goiter. It is only when the patient has been discharged cured and has been perfectly normal for about twelve months, that sufficient inhibition to combat the marked effects of psychic traumata is exhibited.

INFECTIONS IN ETIOLOGY OF EXOPHTHALMIC GOITER

Such general infections as influenza, pneumonia, tuberculosis, and syphilis constitute the exciting cause in one hundred of our series of cases, or about 3 per cent. It would seem that a general infection is coincidental, rather than causal. Possibly the more common cause of exophthalmic goiter, though not elicited, was present but unrevealed by the patient.

The same might be said of focal infections in teeth, tonsils, sinuses, Fallopian tubes, and elsewhere, which in this series presented 67 instances or 2 per cent of the total. Though on general sound principles we must remove diseased tonsils in all goiter patients, these and other infectious foci probably play but a contributory etiological rôle in exophthalmic goiter. Tonsillectomy with the expectation of curing exophthalmic goiter is usually disappointing; this procedure should be regarded as merely supplementary to more direct therapeutic measures in the management of the disease. Bearing in mind the possibility of aggravating the symptoms of the disease by added shock, the time when tonsillectomy should be performed and the nature of anesthetic to be employed should receive due consideration.

IODINE INGESTION IN ETIOLOGY

The publicity to further the use of iodine through the ingestion of this drug in drinking water, iodized salt and in innumerable other forms, with a view to the prevention of goiter, has resulted in so many instances of harm that the medical profession is awakening to the importance of raising a protest against unguided and indiscriminate administration of this substance. Through its tendency to increase the colloid content of the thyroid gland, iodine very frequently increases the size of simple and of hyperplastic goiter of Graves' disease to an alarming degree. Through its tendency toward whipping up the function of the thyroid, iodine is capable of converting a simple adenoma into a toxic one, and a toxic hyperplastic thyroid into one whose hyperfunction knows no bounds and endangers the life of the individual. While the majority probably are capable of withstanding iodine ingestion, a percentage of individuals susceptible to exophthalmic goiter react in a manner almost corresponding to the infliction of psychic trauma. One hundred patients of our series (over 3 per cent) presented a history in which no exciting cause was discoverable other than the ingestion of iodine for the cure of an imaginary or actual slightly swollen thyroid. The discovery of the existence of an unduly palpable thyroid gland leads to a kind of goiter phobia, and then follows the ingestion of iodine either through the busy medical attendant, or through self-administration induced by popular literature and advertisements.

INGESTION OF THYROID EXTRACT IN ETIOLOGY

What has been stated respecting iodine may be doubly emphasized regarding thyroid extract. The unfortunate tendency of today in the direction of becoming and remaining thin to keep pace with the dictates of dame fashion has resulted in an avalanche of obesity "cures" described in newspapers and magazines. Nearly all contain thyroid extract, iodine, or both. Those containing thyroid extract must of necessity possess its iodine content. Thirty-three patients, or one per cent of our series presented a history of the ingestion of thyroid extract as the only explicable reason for the development of the disease.

One might rightly ask: If thyroid extract is more capable

of producing exophthalmic goiter than is iodine, why so comparatively few cases of the disease from ingestion of thyroid extract? The answer is to be had in the tremendously increased publicity given the use of iodine and iodine-containing nostrums as compared to the publicity given thyroid extract and obesity "cures." Moreover, the effect of thyroid extract ingestion is more prompt and startling. The average patient feeling sick after the taking of a few tablets of thyroid extract becomes alarmed, discontinues it, and may recoil back to the former sense of well-being. Not so with iodine, which may be taken for many months without a realization of resultant harm.

The question again arises: Since thyroid extract ingestion is said by many investigators to be capable only of producing hyperthyroidism in man, how does it produce exophthalmic goiter? The answer lies in the type of individual taking it. In other words, it is *susceptibility* to exophthalmic goiter that is as much the determining factor as thyroid extract.

EXOPHTHALMIC GOITER WITHOUT DISCOVERABLE EXCITING CAUSE

Despite careful history-taking and physical examination, 201 patients (6 per cent of this series), presented no exciting cause to account for the onset of exophthalmic goiter. It is felt that in most of these there existed one or other of the aforementioned exciting causes, probably psychic trauma, but unrevealed by the patient. Though it would seem that a psychic trauma resulting in the development of exophthalmic goiter would make an indelible impression upon the patient's mind, this is frequently not the case, especially when bodily injury was not sustained. In many patients in whom there was an unmistakable history of psychic trauma, this information was obtained only after the second or third interview, or occasionally through an almost psychoanalytical process. It was then that the event suddenly loomed forth in the patient's mind in all its detail, and the history was completed. It is therefore evident that in hasty history taking this valuable information may be lost. Our histories require more than an hour of questioning, and half the time thus expended is devoted to an inquiry into the mental life of the individual. Despite extreme care, it is felt that occasionally a patient has undergone a psychic trauma, the nature of which is distasteful to narrate, hence remains for-

ever unrevealed to the physician. Moreover, we must not overlook the fact that many patients applying for treatment realize the mistake in having taken iodine or thyroid extract prior to the onset of the illness and do not care to discuss this matter. Were we able more keenly to scan the inner life and past experiences of these patients it is very likely that the instances yielding no history of exciting cause would be reduced to zero.

CONCLUSIONS

1. In this series of 3343 cases of exophthalmic goiter, 2842 or 85 per cent presented a clear history of psychic trauma as the exciting cause of the disease. In 167 cases or 5 per cent of the series, there was elicited a history of general or focal infection as the probable exciting cause of the disease. In 133 cases or 4 per cent of the total the ingestion of iodine or of thyroid extract in tablets or in the form of obesity "cures" was regarded by the patients as the cause of the symptoms. In 201 cases or 6 per cent, there was no discoverable exciting cause to account for the onset of the disease.

2. It is felt that in most instances in which infections appear to serve as the exciting cause and in those in which no exciting cause was discovered an unrevealed psychic trauma may have been the exciting cause to account for the onset of the disease.

3. Since psychic trauma appears to be the exciting cause in the vast majority of cases of exophthalmic goiter, it would appear that this factor more closely approaches the solution of the question of its etiology than any other theory.

4. The predisposition or "soil" upon which the exciting cause is superimposed is usually an inherited and occasionally an acquired peculiarity of the individual.

5. These data point strongly to the irrationality of thyroidectomy in the treatment of exophthalmic goiter. Therapeutic approach, to be fundamentally successful, must be broad and seek to establish the proper equilibrium of the involuntary

mechanism of the body through measures directed toward endocrine and mental adjustment. Moreover, recovery must be made conclusive by efforts at increasing the zone of defense against the tendency toward relapse.

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STUDIES OF THE THYROID APPARATUS. XLVIII. AGE, SEX, WEIGHT, AND SEASON AS LETHAL FAC- TORS IN CONDITIONS OF PARATHYROID AND THYROID DEFICIENCY

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A study of the role of the thyroid apparatus in growth and development would be incomplete were there to be omitted an analysis and brief report of the indications obtained with regard to age, sex, weight, and season differences in mortality subsequent to the glandular removals.

Although the number of animals available for this phase of the work is large, the multiplicity of classes into which they are distributed, as seen from table 1, makes conventional statistical analysis impossible. Nevertheless, proper and legitimate arrangements of the data bring out significant differences from which justifiable conclusions may be drawn.

Before setting down the main thesis of the paper, note should be made of certain differences in reaction to the two types of glandular deficiency. From table 2 it is seen that the per cent

TABLE 1

THE DISTRIBUTION OF THE RATS USED IN THIS STUDY ACCORDING
TO AGE, SEX, AND TYPE OF GLANDULAR DEFICIENCY

<i>Age in Days</i>	<i>Thyro-parathyroidectomized</i>			<i>Parathyroidectomized</i>			<i>Totals on Age</i>
	<i>Males</i>	<i>Females</i>	<i>Totals</i>	<i>Males</i>	<i>Females</i>	<i>Totals</i>	
14.....	13	29	42	9	16	25	67
23.....	134	97	231	86	27	113	344
30.....	78	90	168	36	39	75	243
50.....	47	62	109	35	47	82	191
65.....	31	29	60	40	34	74	134
75.....	52	39	91	39	34	73	164
100.....	21	27	48	21	20	41	89
	—	—	—	—	—	—	—
Totals.	376	373	749	266	217	483	1232

mortality is pretty generally less in the parathyroidectomized than in the thyro-parathyroidectomized groups.

TABLE 2

THE PER CENT MORTALITY ACCORDING TO AGE, SEX, AND GLANDULAR DEFICIENCY														
Age in Days	—14—		—23—		—30—		—50—		—65—		—75—		—100—	
	TP	PT	TP	PT	TP	PT	TP	PT	TP	PT	TP	PT	TP	PT
Male	85	78	83	75	83	50	53	52	48	60	56	49	19	14
Female	72	75	73	33	70	64	71	60	48	44	64	50	47	5

TP—Thyro-parathyroidectomized. PT—Parathyroidectomized.

This would seem to indicate that the parathyroid deficiency produces a less harmful effect than does thyro-parathyroid. Consistent with the foregoing is the fact that a like direction of difference occurred in the growth reactions of the two groups. The details are given in preceding papers. This supports the idea that a difference in the degree of nutritional defect is a factor in the production of the difference in mortality rate, as well as in the production of the differences in growth rate. The similarity is further enhanced by the fact that the sex-specific increase in growth sensitivity of the parathyroidless males at puberty (65 days of age), is mirrored by a relative increase in the per cent mortality at this time. On the other hand, as will be shown, initial body weight is undoubtedly a factor conditioning survival (Table 4). Hence, since the body weight of the parathyroidectomized rats at the time of operation was more, on the average, than that of the thyro-parathyroidectomized, and since the greater number of deaths in both groups occurred shortly after operation because of acute parathyroid deficiency it is probable that the chief factor in the lesser mortality rate of the parathyroidectomized groups is rather the greater initial body weight with all that this implies, than the lesser degree of nutritional defect subsequently induced.

With this preliminary differentiation, we can now go on to the other factors. The two types of glandular deficiency will be considered as a single lethal factor. First, because age, sex, weight, and season are inherently conditioners of the general biological substratum, and, second, because the immediate cause of death in the majority of cases is acute parathyroid deficiency.

The Age as a Factor. The per cent mortality of the rats on age is given in Table 2. Now 150 days of age was taken as the end of the period of observation of growth. Hence, the

minimal standard interval between glandular removal and autopsy was 50 days. Therefore those few rats which lived more than 50 days, but died before they were 150 days old, are omitted from the computations.

From the table it is clear that in general a decrease in mortality rate accompanies the increase in age at time of the initiation of the glandular deficiency. Young rats are more liable to death than old ones.

Suggestions of a like difference in dogs were reported by Rosenblatt in 1894 (1), and in sheep by Simpson in 1913 (2). This age difference in sensitivity is correlatable with the occurrence of idiopathic tetany in man. While the origin of this disorder is obscure, it is possible that parathyroid deficiency is a factor (3).

The distribution of my material is such that seasonal influence is discountable in this age tabulation. The difference is a real expression of the influence of age. The occurrence of the relation in several species marks the phenomenon as one of fundamental biological significance. Particularly is this true since it contravenes in direction the usual age difference in sensitivity to poisons (4).

The explanation is elusive.

Some years ago I showed that rats in which instinctive reactions productive of tenseness or heightened muscle tone had been minimized by gentling, were much less liable to death in *tetania parathyreopriva*, than rats in which these emotional attitudes were given their usual play (5, 6). We have here a potentially similar situation. For although all the rats used in these growth studies were gentled from birth on, it is obvious that the younger animals were subjected to this process for a shorter period before the glandular removals. Combining this with the fact that young animals are naturally more excitable, it is obvious that in this series we may well have had a roughly graded decrement in tonal status with increasing age. The two sets of data are thus seen to be consistent.

Such being the case, and until more explicitly definitive data with regard to the causative mechanism of parathyroid tetany are available, a tentative explanation of the age difference in mortality rate can be based on the same general principles as

that given for the difference in mortality rate of the gentled and wild rats.

It is assumed that the tetany which leads to death in conditions of parathyroid deficiency is in part due to a non-disposal of some toxic product arising from muscle-tonus metabolism. If this is so, it would be expected that the younger animals of greater relative productivity of this hypothetical substance, because of greater excitability and consequently greater muscle tonus, would succumb in greater numbers on loss of the protective function afforded by the parathyroids, than would the older rats of lesser activity.

Although fact coincides with theory on both counts, the interpretation is more suggestive than adequate. In any final analysis, the relationship between parathyroid function and calcium exchange, and calcium and neural irritability cannot be neglected (7).

The values in Table 2 give a hint that the onset of puberty is a factor in the shift from the high to the low mortality rate. This is not inconsistent with the foregoing interpretation.

The average corrected length of survival period after the glandular removals at the several ages is given in Table 3. The few values obviously beyond the usual range were omitted from the computations. The table shows that the young rats survived the deficiency longer than the old. This is probably due to the higher rate of metabolism in the young, which presumably would facilitate the disposal of toxic products. The delay is therefore consistent with the interpretation of the age difference in per cent mortality. It is also consistent with the usual age difference in reaction to poisons in general (4).

The Sex as a Factor. From Table 2 it is seen that there is no consistent sex difference in per cent mortality on age. From Table 3 the suggestion is had that the males tend to survive the loss of the thyroid and parathyroids a bit longer than do the females. In general, however, sex differences in mortality are

TABLE 3

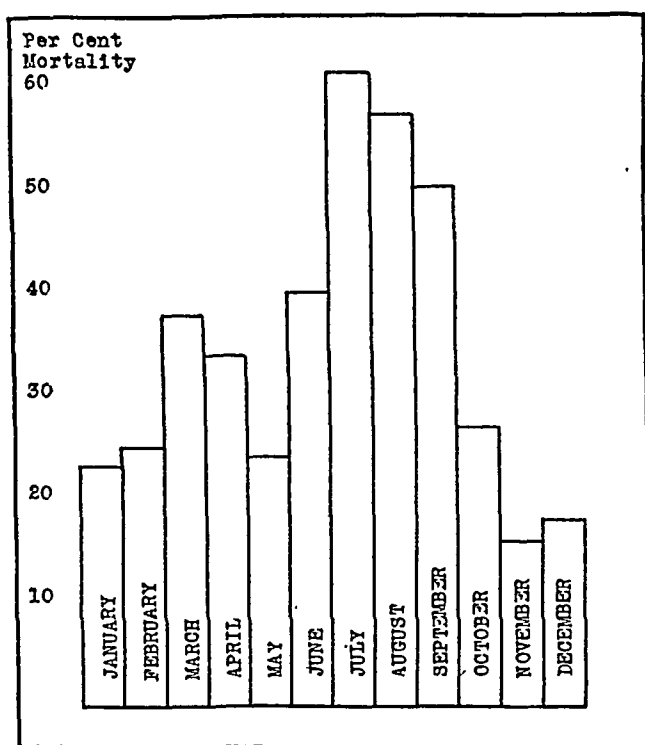
AVERAGE CORRECTED SURVIVAL TIME AFTER THYRO-PARATHYROIDECTOMY AND PARATHYROIDECTOMY AT THE DIFFERENT AGES														
Age in Days	14		23		30		50		65		75		100	
	TP	PT	TP	PT	TP	PT	TP	PT	TP	PT	TP	PT	TP	PT
Male	11	20	7	12	7	7	6	2	4	3	6	4	5	1
Female	11	21	8	9	5	5	3	2	3	3	6	4	5	1

TP—Thyro-parathyroidectomized. PT—Parathyroidectomized.

not demonstrable. Hence sex can hardly be considered as a lethal factor in conditions of parathyroid deficiency.

The Initial Body Weight as a Factor. In Table 4 the average initial body weight of the rats which died during the first three days after operation is compared with that of those which lived until 150 days of age. The three-day interval is taken as the standard, because it is during this period that the large majority of the animals die from the acute effects of the glandular deficiency. No rats dying from the effects of the operative technic were included in the compilation. Only those rats the death of which was due to parathyroid toxemia were used.

Chart 1



The month by month per cent mortality of the rats dying from parathyroid deficiency within three days of the glandular removal.

It is evident that the average initial body weight of the survivors was greater than that of those which died. If body weight is taken as a mark of the general nutritional condition, and such is permissible when groups of rats of like age and source are

compared, it is clear that a sub-average nutritional status is a lethal factor in conditions of parathyroid deficiency.

The Season as a Factor. On Chart I is shown the month by month per cent mortality of the rats dying within three days of the glandular removal.

TABLE 4

AVERAGE INITIAL BODY WEIGHT OF RATS THAT DIED WITHIN THREE DAYS AND OF THOSE THAT LIVED TO 150 DAYS

	Thyro-parathyroidectomized				Parathyroidectomized			
	—Male—		—Female—		—Male—		—Female—	
	Died	Lived	Died	Lived	Died	Lived	Died	Lived
	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.
14.....	14	18	15	19	..	17 [*]	..	20 [*]
23.....	27	29	27	27	27	26	31	30
30.....	43	40	38	39	34	43	33	39
50.....	69	77	74	75	63	74	73	77
65.....	105	119	102	102	104	123	88	104
75.....	118	135	105	113	127	140	96	114
100.....	120	163	127	136	136	160	140	134
Averages	71	83	70	73	82	94	77	83

^{*} Omitted from the averages.

It is evident, from the increased mortality rate, that a decrease in resistance to parathyroid deficiency occurs during the spring months of March and April. This finding is quite the same as that of Cameron and Carmichael (8), who observed that their rats were increasingly subject to tetanic seizures during these months. Furthermore, this increase in sensitivity coincides with the seasonal increase in incidence of idiopathic tetany in man as recorded by Barker (3). The syndromal and seasonal similarity suggest that the latter disorder is associatable with parathyroid deficiency. This idea is further strengthened by the fact recorded in an earlier paragraph, that the age of lesser resistance to parathyroid deficiency in the rats, as evidenced by the high mortality rate, roughly coincides with the age of greater incidence of idiopathic tetany in man. The general correlation is probably more than fortuitous.

Cameron and Carmichael (8) imply in their paper that a fall in barometric pressure accompanied by a sudden marked

rise in atmospheric humidity is a probable cause of tetanic seizures. Unfortunately I am unable to give any data on the atmospheric pressure in relation to the mortality rate in my series. From the chart, however, it is clear that the per cent mortality is markedly increased just during those months when the Philadelphia climate is exhibiting its characteristic exacerbations of humidity and heat. The spread of this combination is rather broader here than in Canada. So the correlation between the two, in my series, is substantial confirmation of Cameron and Carmichael's postulate. The fact that these data are based on records gathered over a period of five years is further support for the interpretation.

These seasonal peaks in mortality are roughly similar in time of occurrence to those observed by Pritchett (9) on the reaction of mice to inoculation with paratyphoid bacillus, and to those observed by Pearce, Brown and Van Allen (10) with regard to the malignancy of implanted tumor tissue. Such being the case, it is assumable that the sensitivity of the animal organism at these times is not specific but general. That is to say, the resistance capacity is lowered, so that any potentially harmful influence is more productive of disturbance than at other times, other things being equal. Whether or not this principle can be extended to man is a matter which can only be solved by a carefully controlled statistical analysis, in which account is taken of regional differences in climate.

CONCLUSIONS

Age and season are factors influencing the sensitivity of the albino rat to parathyroid deficiency. There is good correlation between the reaction to these influences and the incidence of idiopathic tetany in man. This suggests that the latter disorder is associated with a disturbance of parathyroid function.

Since the seasonal increases in sensitivity are not confined solely to reaction to parathyroid deficiency, but are exhibited to a variety of noxious stimuli, it is probable that they represent periods of decreased resistance to any potentially harmful influence.

Initial body weight is also a factor conditioning the mor-

tality rate after parathyroid removal. The per cent mortality is higher in the groups of lower average body weight.

No evidence is available that sex is a factor.

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THE ACTION OF ULTRA-VIOLET LIGHT, THYROID AND PARATHYROID SUBSTANCES UPON AN ARTIFICIAL PLASMA IN VITRO

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This investigation is an attempt to define more clearly the actions which ultra-violet light, thyroid and parathyroid gland substances exert upon the calcium content of the plasma in the body, with special reference to the changes which occur in rickets. The prevalent views of the actions of these agents seem to be that the parathyroid glands are responsible for the retention of calcium and the thyroid in part for the loss of calcium from the body. There does not appear to be any very clear definition of the action of ultra-violet light beyond the fact that it is of undoubted value in raising a lowered plasma calcium and in stabilizing calcium metabolism in certain conditions such as rickets. Grant and Gates (1) have shown that hypertrophy of the parathyroid glands occurs in animals which are exposed frequently to ultra-violet light, and it is known that a seasonal hypertrophy occurs in summer. Beyond these points there does not seem to be any very clear relationship between ultra-violet light and the glandular regulating mechanism of calcium metabolism.

The method of investigation was to study the variation in the calcium content of a special solution in the presence of an excess of solid calcium phosphate, before and after exposure to ultra-violet light and the introduction of thyroid and parathyroid gland substance. The conditions of experiment were as follows:

THE SOLVENT

The basis of the solution used was an aqueous saline solution containing 0.6% NaCl, 0.2% NaHCO₃, and 0.1% glucose. To this were added certain organic substances to represent the corresponding groups in the plasma. Dried egg-white was used to represent the plasma proteins, and there were also added

lecithin, pure cholesterol and cholesteryl oleate, the latter to represent the cholesteryl esters of the plasma. Since it was found difficult to work with a solution containing 7 gms. of protein per 100 cc., which is approximately the concentration in the plasma, solutions containing 2% and 3% protein were used. In these the ratio of lecithin and cholesterol fats to the protein concentration was made the same as that found in the plasma. Carbon dioxide was then passed through the solution until pH 7.4 was reached, as determined colorimetrically with phenol red. The solid dibasic phosphate of calcium was then added in increasing amounts, starting with the addition of 12.5 mgm. per 100 cc. of solvent, and increasing by 12.5 mgm. at a time until 200 mgm. were reached. Actually 400 cc. of the solution was used at a time, so that in each experiment a series of flasks were necessary, the first containing 50 mgm. of the added phosphate, the next 100 mgm., the next 150 mgm. and so on. This mixture was incubated at 37°C for forty-eight hours, after the addition of a little chloroform. The hydrogen-ion concentration was then estimated colorimetrically, the solution filtered rapidly and the calcium and phosphorus contents of the clear filtrate were determined after removal of the protein by boiling with an acetic acid and sodium acetate mixture. The calcium was determined gravimetrically as the oxalate and the phosphorus by titration against a standard uranium solution.

It may be objected that the incubation period of forty-eight hours is insufficient to allow of the establishment of a true equilibrium between the solid and dissolved phases of the calcium phosphate, since it has been repeatedly shown that, using a simple saline solution, weeks or even months are necessary for true equilibrium to be obtained. In the present experiments, however, the solvent is not a simple saline solution. Further, there is no evidence to show that after the plasma calcium has been reduced, these long periods of time are required until the normal value is regained. In normal dogs the blood calcium may be rapidly and largely increased by the injection of Colip's parathyroid extract alone, and there is reason to believe that the additional calcium is mobilized from the skeleton. Again, after the blood calcium has been reduced as in the tetany of rickets or after parathyroidectomy to values below those ob-

tained in the present experiments, it may be increased by the use of parathyroid extract or ultra-violet light to a degree and with a rapidity sufficient to abort an imminent attack of tetany. It must be admitted that the adjustment in the body between the dissolved and solid phases of the calcium phosphates is a rapid one and does not require an indefinitely long period of time for its accomplishment. Whether this adjustment represents a complete or a partial equilibrium, is a matter with which the present investigation is not concerned.

In regard to the present experiments, it is evident that a uniform equilibrium has not been obtained in every flask, as may be seen from the calcium values in any of the charts. But in all cases the variation of the points justifies the average curve which has been drawn, and indicates that in each chart an approximate equilibrium has been obtained in the time period used. Since in all cases the medium and all other conditions of experiment were as nearly as possible constant, the curves are reasonably comparable and sufficiently so to determine whether the agents investigated have had any effect upon the medium.

At the two protein concentrations used, the composition per 100 cc. of the solvent was as follows:

	I.	II.
NaCl	0.6 gms.	0.6 gms.
NaHCO ₃	0.2 gms.	0.2 gms.
Anhydrous glucose	0.1 gms.	0.1 gms.
Dry egg-white	2.0 gms.	3.0 gms.
Lecithin	0.06 gms.	0.09 gms.
Pure cholesterol	0.011 gms.	0.018 gms.
Cholesteryl oleate.....	0.014 gms.	0.021 gms.
Initial pH.....	7.4	7.4

THE AGENTS INVESTIGATED

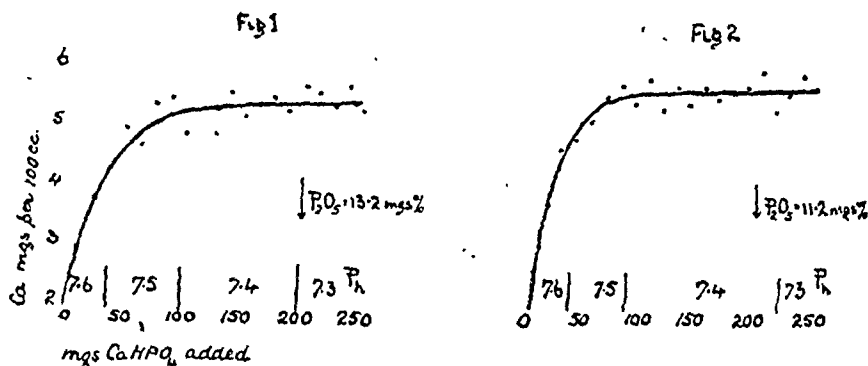
a. *Ultra-violet light.*

Exposure to ultra-violet light was in all cases carried out as follows: Four hundred cc. of the solution were exposed in a quartz flask to the light of a quartz mercury-vapour lamp for fifteen minutes at room temperature with constant shaking. The

distance from the arc was three feet. Irradiation was carried out before the addition of the calcium phosphate and at pH 7.4.

b. *The gland substances.*

Parathyroid and thyroid substances were used in the form of the fresh gland, dried powders and also thyroxin. To each 100 cc. of the solution 8 mgs. of the dry gland or 40 mgs. of the fresh material were added. In the present paper only the results obtained with the fresh gland substance will be considered. Experiments were carried out before and after exposure to ultra-violet light. In certain cases one or more constituents of the solvent were left out in order to determine the one through



which the gland substance exerted its action; these cases will be referred to individually.

THE RESULTS OBTAINED

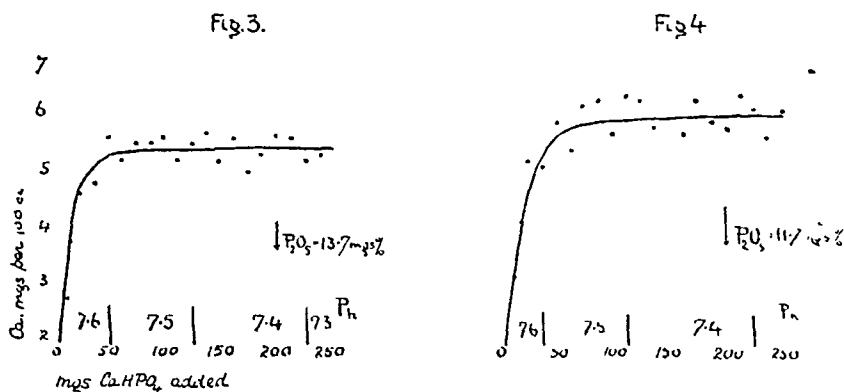
In the accompanying figures the calcium concentrations in the solvent are plotted against the amount of solid calcium phosphate added to the solution. The variation in the reaction of the medium is also shown, and the phosphorus concentration is given in all cases at a value of 200 mgm. of added phosphate. The calcium values actually obtained are shown as points, the curve representing an approximate mean.

Figs. 1 and 2 show the degree of equilibrium attained when the solvent as described was in contact with solid calcium phosphate for the stated time without the addition of any of the agents under investigation. Fig. 1 represents Solution I in the table previously given, and Fig. 2 Solution II. The differences in the two figures are but slight and can be accounted for by

the presence of an additional one per cent of protein in the second solution. These two figures serve as the basis for comparison with the results obtained when the agents under investigation are present.

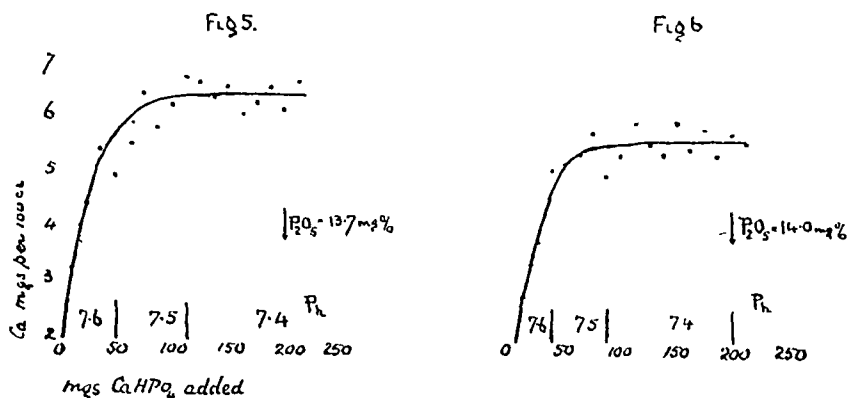
a. *Ultra-violet light.*

The effect of exposure to ultra-violet light is shown in Figs. 3 and 4, comparable with Figs. 1 and 2. The changes induced are only very slight. There is a slight increase in the



calcium content, no change in the phosphorus and a slight shifting of the reaction of the medium to the alkaline side.

The free cholesterol of the medium was then replaced by its equivalent of cholesteryl oleate. The result of exposure of

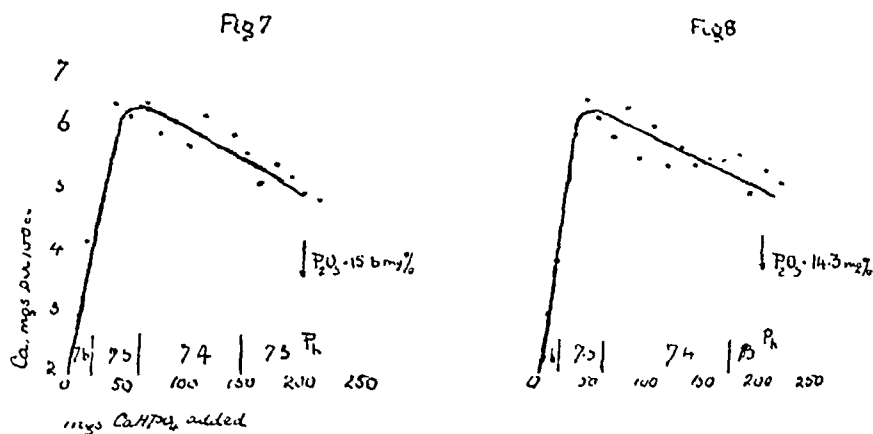


this solution to ultra-violet light is seen in Fig. 5, comparable with Figs. 1 and 3. There is now a definite increase in the calcium content and a shifting of the reaction of the medium to the alkaline side, while the phosphorus content remains un-

changed. On omitting the cholesterol fats altogether (Fig. 6) these changes disappear and a picture very similar to Fig. 1 is obtained; this result was also obtained when the cholesteryl oleate was left out and the pure cholesterol retained in the solution. This would suggest that the action of ultra-violet light is produced through the cholesteryl esters rather than the free cholesterol.

b. Parathyroid gland.

The substance next investigated was fresh parathyroid gland (Figs. 7-11). Figs. 7 and 8 were obtained after the addition of the gland substance in the amount already given and without exposure of the solution to ultra-violet light; they are com-

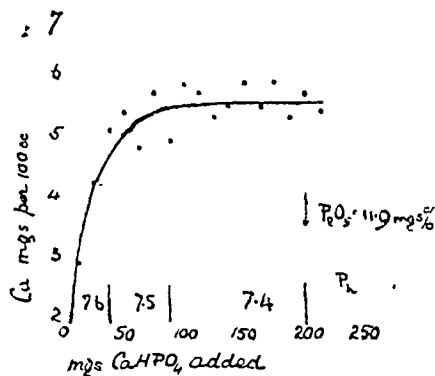


parable with Figs. 1 and 2. There is a definite change in the calcium and phosphorus contents of the solution; the latter is increased and there is a shifting of the reaction of the medium to the acid side. The maximal value of the calcium content of the solution is increased, but it is evident that this happens only on the alkaline side of pH 7.4, for as the acidity of the solution increases its calcium content falls rapidly. In Fig. 9 the experimental conditions were the same as in Fig. 8, except that the cholesterol fats were omitted from the solution. The picture obtained is almost identical with Fig. 2, suggesting that the parathyroid gland produces its effect also through the cholesterol fats.

Figs. 10 and 11 show the effect of the combined action of parathyroid gland and ultra-violet light (cf. Figs. 3 and 4). It is seen that the changes described in the last paragraph have

disappeared. There is a slight but constant increase in the calcium value, the curves are of the usual type, the phosphorus content is reduced, while the range of variation in the reaction of the medium has become similar to that in the two first figures. This would suggest that the ultra-violet light has had a neutralizing effect.

Fig 9.



c. *Thyroid gland.*

On comparison with Figs. 1 and 2, Figs. 12 and 13 show a definite increase in the calcium contents, while the phosphorus remains practically unchanged. There is, however, a considerable shifting of the reaction of the medium towards the acid

Fig 10.

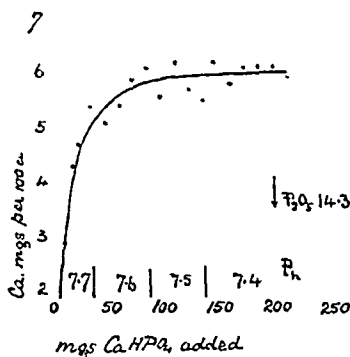
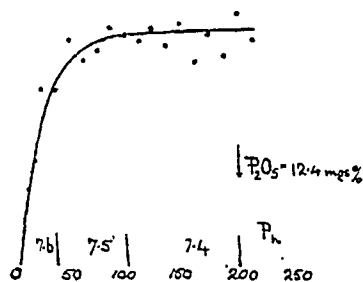


Fig 11



side. After omitting the cholesterol fats from the solution these changes were still present.

After exposure to ultra-violet light (Figs. 14 and 15) the increase in calcium is to some extent maintained. But the alka-

linity of the solution has now been considerably increased and the phosphorus content is lower than in the corresponding Figs. 3 and 4. Again it is evident that the effect of exposure to ultra-violet light is towards stabilizing the reaction of the medium.

Fig 12.

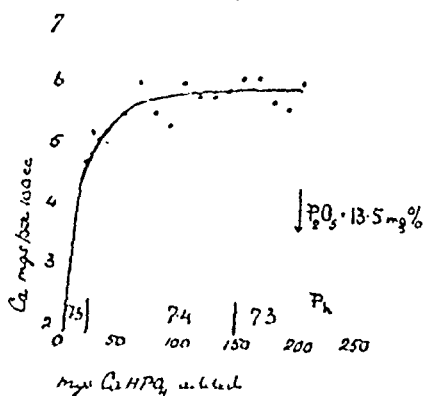


Fig 13.

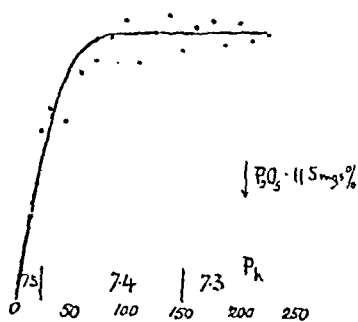


Fig 14.

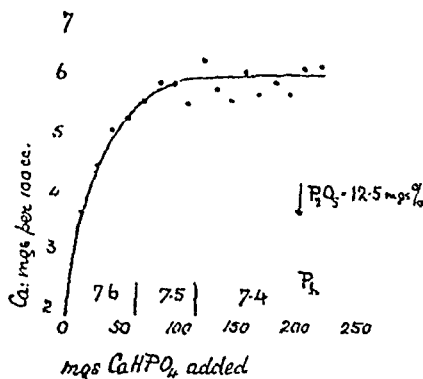
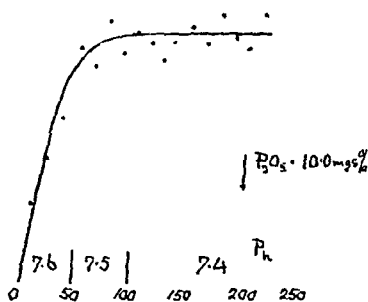


Fig 15.



DISCUSSION

So far as these experiments go, the general conclusions which may be drawn are as follows: parathyroid gland substance increases the calcium content on the alkaline side of pH 7.4, but causes a rapid decrease as the acidity of the solution rises; thyroid substance increases the calcium content of the solution on the acid side, while ultra-violet light in either case has a stabilizing action such that the increases of the calcium contents effected by the gland substances are maintained as maximal about pH 7.4. The effect of the light is shown chiefly by the reduction of the phosphorus contents of the solution, perhaps by some combination between a calcium cholesteryl ester and the

phosphoric ions. This neutralizing effect is seen in each of the three sets of experiments, and it suggests the possibility that ultra-violet light may play some part of importance in the maintenance of the neutrality of the tissues. It is of interest to recall that in nephritic and diabetic acidosis there is a marked disturbance of cholesterol metabolism resulting in a great increase of the cholesterol fats. In nephritic acidosis, in which there is a considerable retention of acid phosphates, the increase in cholesterol fats is due largely to the increase in cholesteryl esters (2). It is of further interest to note that Bergstrand (3) has recorded a small number of cases of nephritis in which parathyroid hyperplasia was present.

The question of parathyroid hyperplasia in conditions which may involve skeletal decalcification is of considerable interest. Pappenheimer and Minor (4) record fourteen cases of rickets with parathyroid hyperplasia, Ritter (5) ten cases and Hartwich (6) twenty-three cases. Erdheim drew attention to the condition in rats rendered rachitic experimentally, while Luce (7) observed it in rats undergoing calcium starvation. Ghiron (8) refers to some thirty cases in the literature of parathyroid hyperplasia in osteomalacia, while Falta (9) considers that parathyroid hyperplasia almost always accompanies this condition. In view of the rarity with which systematic examination of the parathyroids is carried out at autopsies, the association of parathyroid hyperplasia with skeletal decalcification would seem to be an intimate one.

That this hyperplasia is not a defensive attempt to cause increased ossification is indicated by the fact that Korenchevsky (10) failed to find that parathyroidectomy hastened the onset of rickets, and further there is no evidence that true rickets has ever followed simple parathyroid removal. But since there is a continual and excessive loss of calcium from the body, it may be possible that the parathyroid hyperplasia is an attempt to maintain, not the calcium content of the skeleton, but that of the body fluids at the expense of such ossified tissue as there may be. There is no evidence that parathyroid therapy alone will permanently benefit rickets or osteomalacia, just as ultra-violet light fails to benefit permanently the calcium deficiency of parathyroidectomy or of parathyroid tetany. Collip (11) has

indeed succeeded in aborting the onset of rachitic tetany by the use of his parathyroid extract, just as Turpin (12) aborted but failed to cure the tetany in a case of tetania parathyreopriva. The effect, in the former case, at least, may be due to an acceleration of the skeletal decalcification which raises the blood calcium temporarily above that value below which tetany is liable to occur.

Since in rickets there is a greater or lesser deficiency of the ultra-violet factor, the results shown in Figs. 8 and 13 become pertinent to the discussion, on the assumption which is supported both clinically and experimentally, that the thyroid and the parathyroid glands are largely concerned in the regulation of calcium metabolism. In the absence of ultra-violet light (Fig. 13) the thyroid increases the acidity of the solution while the calcium remains fairly constant. But in Fig. 8 it is seen that at the degree of acidity shown in Fig. 13 the parathyroid is not maintaining the calcium level, but is causing a fall of a degree considerably greater than the increase effected by the thyroid in Fig. 13. In rickets the deficiency of the light factor leaves these two glands largely responsible for the regulation of calcium metabolism, and it has been shown *clinically* that not only may parathyroid hyperplasia occur, but that a slight degree of acidosis is not uncommon. The experimental results suggest that the parathyroid glands will maintain an effective calcium concentration only on the alkaline side of pH 7.4 in the absence of ultra-violet light, and it seems possible that this may have some bearing on the decalcification of rickets.

A second parallel between these experiments and the conditions in rickets is seen in the effects of ultra-violet light in the two cases. Ultra-violet light produces permanent benefit in rickets. In the experimental solutions it causes a neutralization of the acidity in the case of the thyroid, and it inhibits the calcium loss from the solution caused by parathyroid action, while it allows the retention of the slight increases of the calcium concentration effected by the presence of the gland substances. It thus seems possible that these experiments may contain the germ of a fresh aspect of the rickets problem, although it is realized that there is a very wide difference between

the conditions in the body and those in the experimental solutions described.

SUMMARY

In a system of the type described there is some evidence to suggest the following conclusions:

1. Ultra-violet light and parathyroid substance both exert their action through the cholesterol fats in the solution; thyroid substance does not do so.

2. Parathyroid substance increases the calcium content of the solution on the alkaline side of pH 7.4. An increase in the acidity causes a decrease in the calcium content. These changes are not observed after exposure to ultra-violet light, with the exception of a slight but constant increase in the calcium content.

3. Thyroid substance increases the acidity of the solution and also its calcium content. The former effect is neutralized by the action of ultra-violet light.

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STUDIES ON VIGOR. XII. THYROID ADMINISTRATION IN SENILITY*

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That the thyroid gland shares in the bodily deterioration of old age is generally believed and the belief is supported by the frequent finding of sclerosis and atrophy in the thyroids of elderly people. That uncompensated thyroid deficiency may play a causal role in the senile picture is suggested by several facts. The symptoms of thyroid deficiency and the manifestations of old age have in common such features as lack of general vigor, dry and scanty hair, dry skin of lowered vitality, dislike of cold weather and decreased mental initiative. In cases of pathologically early senility (progeria) morphological evidence of thyroid deficiency has been reported. Claims, too, have been made that in man amelioration of the common manifestations of old age has been secured by the administration of thyroid substance.

So far as the signs of old age are concerned, the evidence is ambiguous. They might be due in greater or less degree to thyroid changes or merely to deterioration in the body cells themselves. The degenerative changes in the thyroid gland might be merely a part of the general picture of bodily deterioration having no primary significance.

Granting that certain elderly subjects do react favorably to thyroid treatment, the question arises whether such instances are not merely those of thyroid deficiency contracted earlier in life and carried over, unrecognized, into old age. That a considerable number of cases of this sort might be expected to exist is altogether probable in view of the frequency with which hypothyroidism is overlooked, even by good clinicians, both in youthful and adult subjects. A person reaching old age with a pre-existing thyroid deficiency would be likely to manifest certain signs of this in addition to any depression that might

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occur in bodily functions not conditioned by a thyroid factor. On this hypothesis certain subjects might be expected to react favorably to thyroid treatment and others not. It might well be that this therapeutic test would be the only feasible method of detecting thyroid deficiency in the presence of other confusing manifestations of senility.

Whether or not thyroid deficiency is a direct factor in bringing about the manifestations of old age, the possibility that thyroid medication might be beneficial remains open. The impression that this material has a general "tonic" effect is fairly widespread, though its possibilities and limitations are still to be systematically determined. Kerr, Hosford and Shephardson (1926), for example, have recently reiterated the belief, based on several years of clinical experience, that the non-specific stimulating effect of thyroid substance is frequently of value. Other experienced clinicians, on the other hand, have little confidence in thyroid substance as a medicament except in cases of genuine hypothyroidism.

The problem is one that would seem to lend itself better to laboratory than to clinical investigation. So far as the evidence goes it indicates that spontaneous hypothyroidism is rare in experimental animals. Any improvement in the well-being of such animals, therefore, would not be accountable for as amelioration of signs of persistence of pre-senile hypothyroidism.

The revolving cage method is particularly well adapted to an investigation of this problem. Prolonged records of the spontaneous activity of hundreds of rats in our laboratory has shown that this is a sensitive test of the animal's condition. Perhaps the most striking contrast between a young adult and a senile rat is in their respective degrees of spontaneous activity. In our experience healthy males in their most active period average 5000 to 15,000 cage revolutions (yards) a day, whereas old animals may go for days at a time without making 10 revolutions. This is true of animals that, upon casual inspection, seem healthy and vigorous. They are quick and show strong defensive movements and apparently are capable of a great deal more activity than is ordinarily manifested.

METHOD

This report is based on 11 animals to which desiccated thy-

roid substance (Armour's) was fed for varying periods and in varying dosages. Six of the animals were of Wistar Institute stock and five were a hybrid strain of Wistar and wild Norway stock secured from the experimental laboratory of Swift & Co., of Chicago. Four of the animals had been castrated. All were males. Data as to age were not available except for animals No. 585 and No. 879, the ages of which were respectively 12 and 15 months. The others, judged by weight, condition of the hair and activity levels, ranged from one and one-half to two years or more of age.

The animals were kept in revolving cages of the type previously described (Durrant, 1925) and daily activity was taken as the criterion of results.

The dosage of thyroid substance had to be determined empirically. It ranged from 0.1 grain (6.5 mgm.) every other day to 1 grain (65 mgm.) six times a week over periods of from 4 to 26 days. The rats preferred the thyroid substance to their ordinary food, hence no special measures had to be adopted to insure its consumption. With the smaller dosages, however, as a practical means of handling the material it was powdered and mixed in fresh dough made up of some of the ingredients of the standard food mixture (whole wheat flour, milk powder and casein) and fed in pellets containing the requisite amount of thyroid.

RESULTS

In the lower ranges of dosage no effect was secured and in the upper ranges a distinct depressing influence was seen. With no dosage or interval of feeding was any significant beneficial effect detected.

The results of the experiments are set forth in the accompanying table. The daily activity in terms of cage revolutions was determined for 20 days preceding the thyroid feeding. This averaged 1062 turns per day. During the feeding period the average was reduced to 741 and during the 20 days following the feeding period it increased to 928 revolutions. The total amount of gland substance fed ranged from 2 to 13 grains, the average being 9.3 grains. Inspection of the table shows that in all but two cases the average activity was lowered during the thyroid period and in most cases some depression was carried

over into the post-feeding period. In the two instances in which the activity ranged higher during the feeding period the augmentation was well within the range of spontaneous variability in experiments of this type. Similarly, in two instances in the post-feeding period there seemed to be a beneficial after-effect, but this was too slight in magnitude in case of animal No. 3172

TABLE
Effects of Thyroid Feeding on Activity of Rats.

Animal No.	Weights		Average Daily Activity						Total Dosage in Grams
	A. Before Feeding	B. After Feeding	Pre-liminary Period	No. Days	Thyroid Feeding Period	No. Days	Post-Thyroid Period	No. Days	
10*	400	393	1364	20	106	12	710	20	3.5
114*	221	202	541	20	400	26	451	20	2.8
123*	286	284	2371	20	1345	4	2324	20	2.0
585*	240	293	1296	20	1389	26	696	20	3.0
696	333	310	8	20	4	17	3	20	13.0
879	450	464	944	20	601	17	762	20	13.0
3128	392	400	855	20	359	17	382	20	13.0
3129	363	370	748	20	544	17	484	20	13.0
3130	322	330	2268	20	2557	17	1797	20	13.0
3131	290	280	59	20	2	17	922	20	13.0
3072	390	440	1263	20	842	17	1671	20	13.0
Average .	335	342	1065	20	741	17	928	20	9.3

*Castrated previous to the feeding experiments.

to be regarded as significant. Animal No. 3131 averaged 922 revolutions daily after thyroid treatment as against 59 before and 2 during the feeding period. Since, however, this result was not confirmed in four other closely similar cases, and since occasional "sporadic" instances of such changes in activity are seen in untreated animals, the result in the one case is not regarded as significant.

SUMMARY

Eleven senile albino rats, kept in recording activity cages, were fed desiccated thyroid substance over periods of 4 to 26 days.

No beneficial effect as indicated by increase of spontaneous

activity was seen, except in one instance, and this is interpreted as probably accidental.

The series, as a whole, showed depressed activity both during and after the feeding period.

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STUDIES ON VIGOR. XIII. EFFECT OF EARLY CASTRATION ON THE VOLUNTARY ACTIVITY OF MALE ALBINO RATS

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Earlier studies in this laboratory (Hoskins, 1925) showed that animals deprived of their testes after puberty suffered approximately five-fold decrement of their spontaneous activity. Studies of the age factor in this phenomenon were planned some three years ago, when it was first noted. Subsequent studies have shown that the effect of castration is much more marked in rats with a normally high activity level but usually can be demonstrated even when the activity of early adulthood is as low as two or three thousand cage revolutions a day. The effect is seen, also, when toward old age the activity is materially lessened, but still of fair degree.

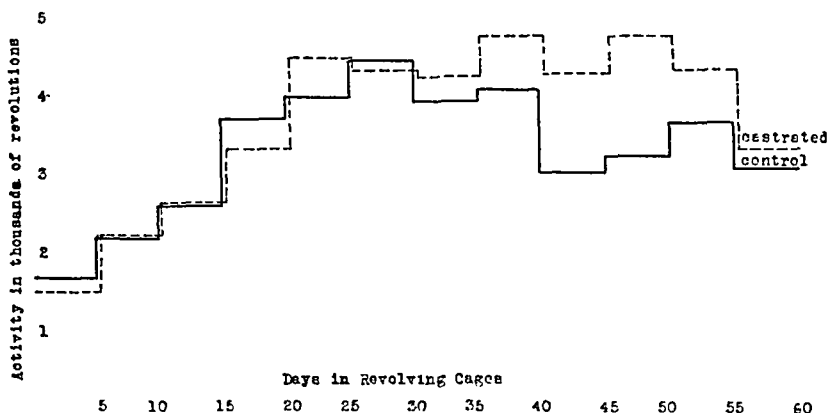


Fig. 1. Average five day activity of normal and castrated rats as manifested by turning revolving cages one foot in diameter.

This paper embodies the results secured when 25 rats were castrated between the ages of 1 and 11 days. Eighteen litter controls were also studied. After castration the animals were then returned to the cages and remained there until they were

TABLE 1
Average Daily Number of Revolutions of 25 Castrated Rats Tabulated Through 12 Consecutive Periods of 5 Days Each.

Animal	Group	Castrated at Age Days	In RC at Age Days	1	2	3	4	5	6	7	8	9	10	11	12
1	1	11	35	1483	1483	1492	1492	1817	1817	2356	2356	1783	1783	1672	1672
3	1	11	35	500	500	810	810	1237	1237	1605	1605	2540	2540	1184	1184
4	1	11	35	3520	3520	1469	1469	1781	1781	4232	4232	2920	2920	2669	2669
5	2	4	27	912	1124	2826	4030	2242	3096	3195	4150	3738	3236	4266	3374
8	2	10	27	456	1228	1328	3034	1850	1701	2146	3938	1516	1576	1280	1305
9	3	7	31	4476	4060	2420	3344	5476	2142	4608	3016	1020	2192	3704	4288
10	3	7	31	3116	3156	3286	5978	2224	5946	4474	4444	3841	3458	4262	4340
14	4	3	24	2620	3416	2444	3188	4614	6808	2178	2210	1372	2888	1792	2174
16	4	3	24	226	2654	2074	3978	8604	10356	6228	9302	8854	13358	8036	7642
18	5	1	23	1962			1150	2260	5548	4810	3774	2804	3016	5032	3934
19	5	1	23	1062	2190	3286	3206	9413	8914	6510	7182	3970	7310	9544	7778
23	6	3	28	34	134	962	1390	1782	2110	2986	2788	2760			
24	7	12	72	1470	2503	2109	2017	1965	2028	1679	1956				
25	7	12	72	494	1058	809	680	1070	930	1612	8059				
27	8	10	26	1498	2632	6984	11618	10042	7528	11052	14004	11628	14530	13500	11112
29	8	10	26	1812	3490	2598	5288	5954	5026	5050	3860	7060	4972	4724	5686
33	9	5	28	3782	6664	10058	7332	9678	10694	11390					
103	10	9	32	1004	1757	2607	2240	6814	6062	6438	6012	5840	6840	7794	
104	10	9	32	723	1331	1942	2006	6240	6982	5040	7536	7394	7770	6668	
109	10	9	32	428	1085	1539	2119	8288	4384	4458	2562	3040	2786	2678	
116	11	10	28	1308	1302	1464	1196	1054	1420	600	1458	856	522	470	860
117	11	10	28	896	1606	3490	7112	6196	1460	1430	2184	4614	5706	2930	5081
118	12	10	23	553	1230	1614	1462	2514	1474	1478	1486	1575	1472	1220	1380
119	12	10	28	1430	2168	2814	5093	5940	6420	6870	6902	2740	3420		
120	13	10	28	2700	2120	2378	2130	2868	2800	2378	3300	3268	2800	3100	2000
Average			7.9	1518	2207	2635	3361	4176	4332	4238	4507	4283	4777	4326	3368

TABLE 2
Average Daily Number of Revolutions of 18 Controls Tabulated Through 12 Consecutive Periods of Five Days Each.

Animal	Group	In RC at Age Days	1	2	3	4	5	6	7	8	9	10	11	12
2	1	35	2893	2893	2494	2494	493	493	1281	1281	407	407	312	312
5	1	35	2890	5042	825	1943	2057	1676	2191	1836	1198	498	640	654
7	2	27	1278	3078	3698	2732	2550	2862	1888	1962	2116	3208	7664	3231
11	3	31	2374	2468	3238	10976	6426	3652	4194	6612	8368	9584	9438	8916
15	4	24	2706	3724	2900	1910	2398	1106	872	3234	3378	1514	1328	1322
17	5	23	2838	3284	4782	5140	6048	6444	6200	5600	3818	4836	8108	5716
20	6	28	484	1534	1510	2654	2372	3562	1478	2140	1485			
26	7	72	175	743	1764	2837	2469							
20	8	26	984	410	1196	5002	1810	1912	40	3972	10088	9568	7120	7496
32	9	28	4480	8190	9212	9664	6192	5072	8452					
105	10	32	428	1103	1976	3465	504	3292	3482	3292				
106	10	32	1838	2212	2901	2134	10790	15794	14004	15454				
107	10	32	1066	826	2186	1802	11200	15236	14088	12544				
111	11	28	416	1118	2020	5470	9678	6194	1988	1192	2876	3628	2950	2512
112	11	28	510	870	1212	3220	3278	4128	2378	2231	1787	2191	2777	2980
113	12	28	360	158	333	272	296	466	464	368	375	224	292	300
114	12	28	2064	2092	2536	1906	1932	1680	1864	1746	1836	1476	1696	1900
115	13	28	2820	2038	2477	2490	2064	2210	1626	2018	2046	1706	1422	2064
Average....		31	1699	2321	2623	3728	4031	4463	3983	4122	3059	3239	3670	3116

weaned at about one month of age. At this time the control and experimental animals were placed in revolving cages, previously described (Durrant, 1925.) They remained in the recording cages for sixty days.

The results of the experiments are set forth in Tables 1 and 2 and in the accompanying graph. These need little comment. While the animals were in the activity cages, the activity was recorded daily, but in the tables average daily records of five days intervals were used. Within the limits of variability of the method, there was no difference between the activity of normal animals and those castrated at an early date.

No evidence has been secured as to what compensatory factors may have come into play to prevent the usual depressive effect of this operation.

I wish to acknowledge my indebtedness to Professor R. G. Hoskins for advice and suggestions in regard to this investigation.

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STUDIES ON VIGOR. EFFECT OF FRACTIONAL CASTRATION ON THE VOLUNTARY ACTIVITY OF MALE ALBINO RATS

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The effect of complete castration on the voluntary activity of the white rat depends upon the period of life at which the animal is castrated. If castration takes place after puberty, the castrated animal begins to lag behind the control. This occurs at about the twelfth day after castration. If the animal is castrated during the first two weeks of life there is apparently no effect on the voluntary activity of the animal.

In this work an attempt was made to study the effect of fractional castration on the voluntary activity. After typing

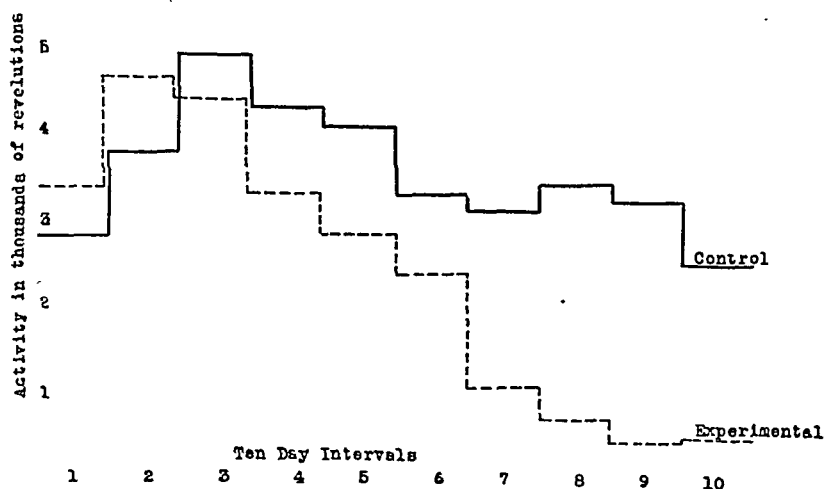


Fig. 1. Graphs of average activity of fractionally castrated animals and their controls tabulated through consecutive periods of ten days each.

the animals, unilateral castration was performed. The effects were observed for a period of twenty days. Then approximately one-half of the other testis was removed. The remaining part was removed in two steps at intervals of 20 days each.

The experiments have not yet been carried to adequate

length. Neither have enough animals been studied, nor have enough intermediate stages between half and complete castration been produced. Circumstances have arisen, however, that compel for the present a discontinuance of the research, hence the data so far secured are put on record for what they are worth.

TABLE 1

Average Daily Number of Revolutions of 18 Fractionally Castrated Rats Tabulated Through 10 Consecutive Periods of 10 Days Each.

Animal	1	2	3	4	5	6	7	8	9	10
30	2563	6720	7273	5844	3838	1775	476	137	201	140
5	2966	5403	6727	3766	2772	1345	627	364	727	230
56	3746	2415	2794	2560	5548	175	14	198	310	319
1	4492	6005	4386	9260	2017	40	22	168	464	
90	4322	8805	2046	1307	1170	897	1182	1334	855	1125
6	4210	5798	8550	6704	1086	1682	600	510	404	512
142	1286	2666	1838	3998	1774	1478	2426	1604	726	538
138	4208	3996	4688	1436	2394	3802	3490	1420	1010	2462
2	6125	5605	2308	4160	1690	624	398	126	348	220
32	5256	3772	2492	1926	1535	476	512	522	1030	428
3	6200	5006	4294	3860	4208	2176	188	426	506	630
142	1104	1418	1398	2476	2874	1592	2132	1718	550	62
56	2550	4124	4650	1890	2610	2936	2848	1754	654	242
46	3256	2990	4940	2445	2438	1892	1660	575	1024	762
90	2734	5054	7926	825	2308	1866	1510	1462	1018	964
137	1308	3550	4156	2268	4912	2508	1164	1230	332	924
106	2184	4614	5706	2930	5081	13156	1486	1486	630	506
68	4674	7170	5000	3840	5164	3196	1078	630	392	868
Average.....	3510	4725	4509	3416	2968	2312	1212	870	621	625
% deviation from controls.....	19.8	20.9	10.0	22.7	29.7	32.9	62.3	75.6	81.5	76.4

Period 1 Typing period.

" 2-4 One testis removed.

" 4-6 One and one-half testes removed.

" 6-8 One and three-fourths testes removed.

" 8-10, Inc. Both testes removed.

Several factors make a statistical study of this character difficult. Castration affects the voluntary activity of the rat to varying degree in different strains and even in different

members of a given litter. Thus the effect is quite marked in the case of the Wistar rat, while the Swift animal, Wistar-Norway hybrid, is much less affected. In the latter the fall in activity is rather slow and never attains as low a level as in the case of the castrated Wistar animal.

The accompanying tables and figure show the results obtained. It will be observed that before the operation the average activity of the experimental group was 19.8% higher than that of the control. Removal of one testis resulted in a reduction of activity from the original level to 10.9% higher than

TABLE 2

Average Daily Number of Revolutions of 15 Controls Tabulated Through 10 Consecutive Periods of 10 Days Each.

Animal	1	2	3	4	5	6	7	8	9	10
18	3635	4832	3845	2823	9831	4043	4600	4716	2962	1681
34	2522	3207	8775	3805	3570	4709	3909	2226	1932	2347
33	3762	5870	6783	6688	1788	1156	2053	2260	2809	3425
112	4129	4793	4046	3160	3989	4146	2015	2815	2821	3094
64	364	4337	5674	11962	8475	5185	4602	3442	3683	3361
11	4942	4566	2516	5546	4730	3250	3634	3692	2872	2758
106	606	3490	7112	6196	1460	1430	2184	4614	5706	2930
139	3656	4376	7262	5886	7068	6570	6158	2854	1844	3716
10	2758	1802	2708	1884	1614	1740	1212	1252	1190	
135	1857	4239	4350	2247	1144	1384	1540	1764	1176	1462
90	2170	2348	2124	1490	4862	3066	3250	4494	6726	4936
106	4804	7974	9087	5120	6362	4742	3452	5550	3774	2442
81	1006	1642	1790	1498	2396	2934	1976	2322	2756	3308
5	2088	3726		5896	4246	4246	5206	7480	8284	1152
113	1638	3392	4070	3075	2838	3124	2520	2646	1938	3194
Average	2929	3908	5010	4418	4224	3448	3220	3575	3362	2653

that of the control for a period of twenty days. After the second operation, in which half of the remaining testis was removed, the activity dropped to 26.2% less than the control level. During the third twenty-day period where one and three-fourths testes were removed, the activity dropped to 47.6% below the control level. After the complete removal of both testes the

average activity observed for a period of thirty days was 78.8% less than that of the level of the controls.

SUMMARY

A study of the effect of fractional castration of the voluntary activity of the rat was made. It is shown that fractional castration conditions the activity of the animal. The fall in activity after removal of one testis was slight. The most marked changes were observed after removal of the last fraction of the second testis.

I wish to acknowledge my indebtedness to Professor R. G. Hoskins for advice and suggestions in regard to this investigation.

Abstract Department

Changes in inorganic constituents of blood in suprarenalectomized cats and rabbits. Baumann (E. J.) & Kurland (S.), *J. Biol. Chem.* (N. Y.), 1927, **71**, 281; *Abst. J. Am. M. Ass.* **88**, 1034.

In the experiments done by Baumann and Kurland, evidence did not point to an alkalosis as one of the consequences of suprarenalectomy. Suprarenalectomy does cause a fall in plasma sodium and chlorides. In the cat, a rise of plasma potassium, magnesium and, occasionally, calcium has been found. In a few other conditions in which suprarenal injury occurs, it has been found that a decrease in sodium and chloride content of plasma also occurs.

New research on the action of extracts of the adrenal gland on muscular fatigue (*Nouvelles recherches, sur l'action des extraits de capsules surrenales sur les muscles fatigues*). Ferreira de Mira (M.), *Compt. rend. Soc. de biol. (Par.)*, 1926, **95**, 1284-1285.

Fresh extracts of mammalian adrenals were injected into the dorsal lymph sac of frogs whose gastrocnemius muscles had been fatigued. The result—a remarkable recovery of the contractility of those muscles—appeared to be due to epinephrin because the latter alone was just as effective. Solutions (2 cc.) of 1:100,000 of epinephrin caused greater amplitude of the contraction and postponed the onset of fatigue considerably.—J. I. Evans.

Blood calcium and adrenalin action (*Blutkalk und Adrenalin wirkung*). Frisch (F.) & Fried (E.), *Wien. Klin. Wchnschr.*, 1926, **39**, 1389-1391.

The authors compare the blood calcium concentration to the hemodynamic effects of epinephrine injections. In the human subject conditions with low blood calcium make for a more powerful blood pressure rise from epinephrine than in instances of normal or high blood calcium. This inverse proportionality is taken to denote a dependent relationship between sympathetic irritability and blood calcium concentrations.—A. L. Tatum.

Influence of yohimbine on splanchnic nerve action and of nicotine on adrenal secretion. Houssay (B. A.) & Molinelli (E. A.), *Rev Soc. Argent. Biol.* (Bs. Aires), 1926, **2**, 26-32. *Compt. rend. Soc. de biol. (Par.)*, 1926, **95**, 808.

In dogs deprived of their adrenals the inversion of the pressor

vascular response to splanchnic stimulation, produced by the action of previous injections of yohimbine, was still retained. The hypertensor effect of extracts of glands of the scorpion (*Buthus quinques-triatus*) persisted unaltered. By the method of suprarenal-jugular anastomosis in dogs it was observed that an intravenous injection of yohimbine did not produce adrenal discharge. The hypertensor effect of splanchnic stimulation and injection of nicotine gradually became less and then ceased, although a slight increase of adrenal secretion that raised the arterial pressure and contracted the spleen of the recipient dog was still produced. The adrenal-secretory effect of the splanchnic was more resistant than the vaso-constrictor effect. —Author's Abst.

The blood supply and weight of the adrenal glands and their relation to body surface and body weight. Houssay (B. A.) & Mollinelli (E. A.), Rev. Soc. Argent. Biol. (Bs. Aires), 1926, 2, 117-129.

In 100 male dogs (weight 10 to 38 kg.) the blood supply of the left adrenal was proportional to the body weight. The average amount of blood passing through the left adrenal was 0.345 cc. per kg. per minute. The weight of the left adrenal was not proportional to the body weight, but approximately to the body surface. A similar relation is shown by the data of Langlois for dogs and by that of Donaldson for male rats. In female rats (Donaldson) the adrenal weight is more nearly related to body weight. The significance of these results is discussed.—Author's Abst.

Blood sugar, glucose consumption and formation of glycogen after removal of suprarenals. Pico Estrada (O.), Semana méd. (Bs. Aires), 1926, 33, 1653; Abs. J. Am. M. Ass., 88, 1041.

In experiments on dogs by Pico Estrada the blood sugar fell after removal of the suprarenals. At death, hepatic and cardiac glycogen had diminished considerably; the decrease in muscular glycogen was also pronounced, but not so great. After intravenous injection of dextrose there was little change in the hepatic glycogen, and the glycogen in the muscles and heart increased only slightly. In suprarenalectomized animals, the blood in the femoral vein contains as much glucose as does the arterial blood. Suprarenalectomy seems to bring about a disturbance in the metabolism of the carbohydrates, decreasing the glycogen function of the liver.

Ovarian hormone in the blood (Untersuchungen über das Ovarialhormon im Blute gravidier und nichtgravidier). Fels (E.), Klin. Wchnschr. (Berl.), 1926, 5, 2349.

A considerable series of tests of blood serum from non-pregnant and pregnant women were made in spayed mice, using the

oestrous reaction of the vagina as a criterion of the presence of ovarian hormone. Serum taken during different stages of the menstrual cycle was uniformly negative. Negative results were obtained during the first few months of gestation. Later in pregnancy the majority of tests were positive. Apparently a conclusive demonstration of the presence of this hormone in the blood during the latter half of gestation.—E. Allen.

Precocity of endocrine origin (Beitrag zur endokrin bedingten Frühreife—Interrenal-genitales Syndrom). Herschmann (H.), & Neurath (R.), *Wien. klin. Wchnschr.*, 1927, **40**, 277-279.

A description is given of a 11-year-old girl with the stature of about 16 years. There is a history of lues in her mother and mother's mother. Development was normal until three years of age, when there appeared a remarkable acceleration in growth, pubic hairs, enlargement of the clitoris and a hesitancy in the gait which became worse after 4½ years of age. When nearly 5 years old she began to have fever, night sweats, and a cough. At 5 years of age, when admitted to the out-patient department, she was lively and talkative, slender in build, 117 cm. high, with a reach of 113 cm.; 63 cm. in sitting height, 51.5 cm. in head circumference, and 21.5 kg. in weight. She had a cerebellar-ataxic gait, positive Rhomberg, exaggerated tendon reflexes in lower extremities with indications of petellar clonus on both sides. No visceral abnormalities were found. Mons veneris and labia majora were covered with hair. The clitoris was 2.5 cm. long. Inner genitalia were not palpable. There was no abnormal hair development in other parts of body. Mammary glands were not developed. Urine was normal. Wassermann was negative and X-rays of hand and head were negative. The present status of the child at 12 years of age: Strong and muscular; fatty deposit noticeable only on mons veneris; much hair on legs, especially below the knee; axillary and pubic hairs as in adult female; well developed mustache; teeth irregular and defective; height, 152 cm.; reach, 159 cm.; sitting height, 89 cm.; weight, 49.6 kg.; head circumference, 56 cm.; lower portion of the body was too short for upper portion; the larynx was slightly prominent and the voice was coarse; there were no visceral abnormalities; nervous status was negative except for a positive Chvostek's sign and slight exophthalmus; all evidence of ataxia was absent; the intelligence was that of a 7-year-old child; there was a negative Wassermann and the X-rays of the head were negative; mammary glands were not developed; the clitoris was 4 cm. long and the vagina 9 cm. long; a mass about the size of a cherry (probably uterus) was palpable through the rectum; there was a body about the size of a bean in the region of the left ovary and on the right was found a smooth, almond-shaped movable mass; no ligaments could be felt. Abderhalden's reactions were interpreted as

indicating defective hypophysis (both lobes), thymus, suprarenal cortex and ovary, but normal thyroid and pineal. The case is discussed especially from the point of view of suprarenal cortex and gonad disturbances.—A. T. R.

Internal secretions of ovary: III. Effects of injection of oestrin during lactation. Parkes (A. S.) & Bellerby (C. W.), *J. Physiol.* (Lond.), 1927, 62, 301.

A mouse suckling a litter of more than two does not come into oestrus (except for the post-partum period) during normal lactation. The corpora lutea of the post-partum ovulation are persistent and probably oestrus inhibiting. Injection of the oestrus producing hormone during lactation induced oestrus, at which copulation would take place. The amount required showed a close correlation with the number of young suckling. Where litters of 7 were suckling, as much as 10 mouse units of oestrin were required. When only 2 were suckling, oestrus was spontaneous. No pregnancy was observed to follow copulation at the induced oestrus period. Ovaries sectioned after copulation showed no young corpora lutea. It is concluded that ovulation did not occur during the artificial period. Mice ovariectomized early in lactation required only small amounts of oestrin (2 mouse units) to produce oestrus, whatever the size of the litter suckling, so the inhibitory effect of lactation is set up via the ovary and probably via the persistent corpus luteum. The dosage of oestrin required to over-ride the corpora lutea of lactation is greater than that required to over-ride the corpora lutea of pregnancy.—M. O. Lee.

The effect of the testis on metabolism in the chicken (*L'influence du testicule sur le métabolisme chez les Gallinacées*). Szuman (J. G.), *Compt. rend. Acad. de sci. (Par.)*, 1926, 183, 1053-1055.

The amount of food ingested, the amount of excreta and the nitrogen balance per day was studied in normal chickens, capons, and capons with testicular grafts. The amount of food voluntarily eaten and the amount of excreta given off by the capon were about 50 per cent that by the normal male. In capons with testis grafts the amount of food eaten and the amount of excreta were practically the same as in the normal male. Even with testis grafts amounting to only one-tenth of the average testicle, no differences were found. Cocks with one testicle removed gave the same results. Data as to the minimum maintenance level of nitrogen intake were not obtained.—M. O. Lee.

The unity of multiplicity of the autacoids of the posterior lobe of the pituitary gland. Draper (W. B.), *Am. J. Physiol.* (Balt.), 1927, 80, 90-99.

Abel's conclusion that the various pharmacological effects of

pituitary extract are due to a single substance is challenged. It was found that the pressor and oxytocic activities have a widely differing distribution during normal butyl alcohol extraction. The results of Dudley and of Schlapp are thus confirmed. The renal activity followed closely the pressor activity during normal butyl alcohol extraction. The separation by extraction of the oxytocic activity from the renal and pressor activities is explained by assuming that the hormone responsible for the oxytocic activity is chemically separate from that responsible for the pressor and renal activities. The data obtained do not warrant a conclusion as to whether the pressor and renal activities are due to one or more than one substance. A bladder fistula method of assaying the renal activity of posterior lobe extracts is described. This method, although time-consuming and possessing a rather large margin of error, may, in the absence of a better one, be of some use in standardizing this activity.—R. G. H.

Structure of the pars intermedia of the hypophysis in man (*Sulla struttura della pars intermedia dell'Hypophysis cerebri dell'uomo*). Guizzetti (P.), Arch. d. Biologia normale (Fiernze), 1927, 80, 665-735.

The hypophysial fissure remains open in man until about 16 years. Tubular glands are regularly present at birth. They secrete sero-albuminous materials, beginning in fetal life and ending at about the time of puberty. Evaginations of the hypophysial fissure arise from the ventral wall of the fissure at its cephalic extremity and penetrate deeply into the transition zone from the pars intermedia to the tongue-like process. They are special formations, of a different nature than the rest of the fissure and largely coalesce to form the cysts of the pars intermedia. The epithelium of the evaginations begins to differentiate toward the end of the first year of life. Two varieties of cells are described. The evaginations secrete substances which, by their histo-chemical reactions, must be classed with the mucins. This secretion begins only after one year from birth and continues thereafter, more or less constantly throughout life. The cysts of the pars intermedia are derived from three sources: from segmentation of the fissure; from the tubular glands; from the evaginations of the fissure. The cysts derived from the last two sources present different morphological characters by which it is easy to distinguish one from the other.—W. J. Atwell.

Studies on the anterior lobe of the pituitary body. Johns (W. S.), O'Mulvenny (O.), Potts (E. B.) & Laughton (N. B.), Am. J. Physiol. (Balt.), 1927, 80, 100-106.

Extracts of the anterior lobe of the pituitary body of the ox, when injected into healthy adult dogs (number not stated), caused

hyperglycemia, polyuria and glycosuria. Renewal of the treatment gave polyria and glycosuria, but no hyperglycemia. The hyperglycemia is ascribed to increased glycogenolysis in the liver, since no glycogen was found in the liver of the treated animals. It is deduced that the threshold value of the kidney for glucose was lowered as a result of the administration of the extracts. The action of extracts on blood pressure and uterine strips was not similar to the action of "pituitrin." Extracts of liver and muscle made by the same process as the extracts of the anterior lobe of the pituitary body, failed to give similar results when administered to healthy adult dogs.—R. G. H.

The induction of precocious sexual maturity by pituitary homeo-transplants. Smith (P. E.), *Am. J. Physiol. (Balt.)*, 1927, 80, 114-125.

It was found that daily homoplastic transplants of the pituitary from the adult, given intramuscularly, induced sexual maturity in the female rat as early as the weaning date (22 days of age), this transcending all normal variability. Animals which are but 14 days of age when treatment is begun mature sexually in from 8 to 10 days; when the treatment is begun at the weaning date they mature in five or six days. The opposite response of the sex apparatus results from pituitary ablation before sexual maturity, the complete establishment of the vaginal canal being delayed and the genital system remaining undeveloped. The anterior pituitary component of the transplant only, is essential for the induction of premature sexual maturity, the posterior lobe of the pituitary neither hindering nor aiding in the response. No stimulus to the development of the uterus or vagina of the immature ovariectomized rat is given by these transplants. The invariable and rapid maturity which is induced by daily pituitary transplants speaks against the view of those who maintain that hypophysectomy does not interfere with sexual development or function, and indicates an important hypophyseal-gonadal interrelationship.—Author's Abst.

Treatment of diabetic coma.—Chabanier (H), Lebert, Lobo-Onell & Lumiere. *Presse méd. (Par.)*, 1927, 35, 83; *Abst. J. Am. M. Ass.* 88, 1040.

The authors consider the two phases in diabetes, the precomatose and that of established or "confirmed" coma. In the first phase acidosis is due exclusively to excessive formation of acetone bodies. In the other phase there is retention of acetone in the kidney, due to disturbed function of that organ. The phenomenon is revealed by deficient micturition associated with low concentration of urea in the urine and hyperazotemia. While insulin alone suffices in the precomatose phase, in comatose conditions diuretics and cardiac stimulants should be given in addition. Of 28 cases of diabetic

coma, only two resisted insulin treatment. Nine patients died, in spite of the subsidence of acetonemia and recovery from coma.

Artificial hibernation in the woodchuck (*Arctomys Monax*). Dwor-kin (S.) & Finney (W. H.), *Am. J. Physiol. (Balt.)*, 1927, **80**, 75-81.

When a woodchuck is given an amount of insulin sufficient to produce profound hypoglycemia, it loses its power of temperature control. If it then be placed in an environment even moderately cool, it passes into a state of artificial hibernation. The characteristics presented by an animal in this condition are: the woodchuck becomes poikilothermic; it is unable to shiver or execute spontaneous movements; consciousness is lost, and the animal is insensible to painful stimulation; the convulsions associated with insulin hypoglycemia do not occur; the metabolic rate is greatly decreased. The state of torpor thus induced can be prolonged by the administration of insulin at intervals. The injection of glucose terminates this condition. Shivering begins almost immediately, the temperature rises at a rapid, though variable, rate, and the animal returns to normal.—Authors' Abst.

Activation of insulin (Über Aktivierung von Insulin). Glaser (E.) & Halpern (G.), *Biochem. Ztschr. (Berl.)*, 1926, **177**, 196-205; *Abst. Physiol. Absts.*, **12**, 41.

The oxidase obtained from eosinophile granules of the blood and kinase obtained from the small intestine function as activators of insulin, whilst peroxidase from bone marrow and liver aldehyde are inactive. Irreversible inactivation of insulin is observed by treating with aluminium hydroxide. Alteration of pH does not markedly affect insulin action. Tyrosinase and peroxidase of horse-radish have no effect, but yeast juice boiled for 8 hours has a marked activating effect on insulin.

Insulin treatment. Holzer (H.) & Klein (O.), *Deutsches Archiv. für klinische Medizin (Leipz.)*, 1926, **153**, 129; *Abst. J. Am. M. Ass.*, **88**, 1042.

Holzer and Klein had good results in treatment of grave diabetes with large doses of insulin (100 units or more) and of carbohydrates (from 120 to 200 gm.). The patients improved rapidly and the insulin dose was soon reduced. The authors attribute the improvement to a formation of carbohydrate reserves and suggest the preventive use of the treatment in patients with grave and moderately grave diabetes. It would be necessary to repeat the course several times a year.

Diabetes. One thousand cases. John (H. J.), Arch. Int. Med. (Chicago), 1927, 39, 67; Abst. J. Am. M. Ass., 88, 1032.

One thousand cases of diabetes are analyzed by John. The incidence of syphilis in this series was 2.6%. There was an hereditary history of diabetes in 4.6%, and a familial history in 5.1%. The highest blood sugar level on admission was 908 mgm. per hundred cubic centimeters. Blood sugar figures as high as 310 mgm. per hundred cubic centimeters were encountered without glycosuria. The diabetic renal threshold was high in many cases. The general belief that insulin once used must always be continued is shown to be fallacious by the cases in which good progress has followed the discontinuance of insulin. The mortality rate in 35 operations on diabetic patients in this series was 20%. By the exclusion of 4 cases in which death was due to septicemia, which was present at the time of operation, or to inoperable carcinoma, the mortality rate is reduced to 8.5%. There were 28 cases of diabetic coma. The blood sugar in these cases ranged from 200 to 810 mgm. per hundred cubic centimeters; the plasma acetone from 0 to 3 plus, and the plasma carbon dioxide from 44.3 to 9.9 mm. of pressure. The higher figures in the last instance were due to the administration of insulin previous to the carbon dioxide determination.

Physiological ideas on vagotonia (pancreas and vagal tonus). Santenise, Tr. Reunion Neurologique, Paris, June, 1926; Arch. Neurol. & Psychiat. (Chicago), 1927, 17, 271.

Vagotonic persons have a remarkable tolerance for carbohydrates; on the other hand, those with hypotonia have a low tolerance. In patients in whom vagotonia fluctuates, there are parallel fluctuations in carbohydrate tolerance. The injection of insulin seems to have a stimulating effect on the pneumogastric, analogous to the action of epinephrin on the sympathetic system. Following injections of insulin there is slowing of the heart, exaggeration of respiratory arrhythmia, increase in the amplitude of contraction due to the lengthening of the diastolic phase and exaggeration of the oculocardiac reflex. This vagotonic action of insulin is immediate and is not modified by raising the sugar in the blood by injection of glucose, showing that insulin is a specific excitant for the parasympathetic system. In experimental animals the vagal tonus seems to run parallel with the size and weight of the pancreas, animals having large glands being largely vagotonic. In the circulating blood there is a hormone that exerts this vagotonic action; the serum coming from the pancreatic vein is extremely active. Blood drawn two hours after pancreatectomy is inactive.

Simplification of the dietetic treatment of diabetes mellitus. Winn (R. C.), Med. J. Australia (Sydney), 1927, 1, 321-325.

An attempt has been made to simplify the details of the dietetic treatment without sacrificing any of its principles. Rest to the islands of Langerhans continues to be the essential principle and this can best be secured by a moderate reduction in the diet, without "insulin" in the majority of cases and with "insulin" if sufficient food to do light work cannot be supplied otherwise. The Allen method is ineffective in emaciated patients, unnecessary in others and because of starvation (and consequent lowered resistance to infection) obnoxious and harmful in all. Though the Allen method has been superseded, unnecessary detail associated with it has been retained by many. In the method here described the patient is examined once a week and increases of 200 calories are made in the diet if the urine is "sugar-free." By varying combinations of three "diet groups" (of 500, 600 and 900 calories), it is possible to supply completed diets ranging from 1,000 calories to any limit, with rises of one hundred up to 2,000. Just as it is the custom in lists of vegetables and fruits to strike averages for the carbohydrate content, so for meat and fish average figures have been used. Only a few exceptions and alternatives have been listed.—Author's Abst.

Use of parathyroid extract in hemorrhage. Gordon (B.) & Cantarow (A.), J. Am. M. Ass. (Chicago), 1927, 88, 1301-1302; Abst. A. M. A.

In the prevention and treatment of 347 cases of hemorrhage arising from various sources, the authors employed parathyroid extract, from 10 to 15 units every thirty to thirty-six hours, except in a few instances in which from 15 to 20 units were administered every twenty to twenty-four hours. The plan of treatment was to continue the injections until cessation of hemorrhage occurred, and then to administer one dose after thirty-six hours. So far as possible other treatment was discontinued. The series includes hemorrhage from the following sources: the respiratory system, the majority of which were instances of pulmonary bleeding; the gastrointestinal and genito-urinary tracts, and operative incisions in various parts. The extract was also administered to patients with jaundice, and in other conditions in which the clotting time of the blood was prolonged. Cessation occurred in 304 patients, following one or more transient increases in the calcium content of the circulating blood. The most favorable results followed the administration of from 10 to 15 units every thirty-six hours for one to three doses. As a preoperative measure in jaundice, it reduced the coagulation time to within normal limits and apparently prevented hemorrhage. The unfavorable results occurred when over-

dosage and prolonged administration were employed. In addition, unfavorable results occurred in blood dyscrasia (puerperal hemorrhage and hemorrhagic disease of the new-born) irrespective of the size and number of doses, apparently because of certain local changes in the tissues. As compared with the common experiences with oral and intravenous administration of calcium the results are more dependable, and furthermore gastric irritation and other untoward effects are avoided. The hormone was found to be of special value in patients recovering from surgical operations who were unable to tolerate oral therapy. The use of parathyroid extract is suggested as a means for controlling hemorrhage because it effectively mobilizes calcium salt, which is normally stored in the body and which is necessary for clotting.

Tetany and syphilis of the parathyroids. Langeron (L.) et al., *Presse méd. (Par.)*, 1927, **35**, 81; *Abst. J. Am. M. Ass.*, **88**, 1040.

In the authors' case, a man aged 47, was admitted to the hospital for digestive disorders followed by decrease in calcium and an increase in the alkali reserve. Necropsy revealed, among other lesions, gummas in the lungs and syphilitic sclerosis of the parathyroids. The changes in the liver and in the kidneys were insignificant. The corpus striatum appeared almost intact. Lesions of the parathyroid could be responsible for alkalosis and hypocalcemia, which, in turn, might induce neuromuscular hyperexcitability and tetany. Derangement of gastric secretion from chronic alcoholism appeared as a contributing factor in this case.

Occurrence of parathyroids on anterior surface of thyroid gland. Millzner (R. J.), *J. Am. M. Ass. (Chicago)*, 1927, **88**, 1053-1055; *Abst. A. M. A.*

During a period of six months, 162 thyroidectomies were performed at the University of California hospital. In twenty of these cases one parathyroid was removed, and in one case two parathyroids were removed. The author gives assurance that all but six of the twenty-one parathyroids were checked and proved by microscopic study of a small fragment. The six that were not checked were typical in every respect, and grossly looked exactly like those that were checked. In none of the cases did the patients develop any clinical signs of tetany. Studies are now being carried on with autopsy material. In approximately 10% of normal thyroids, one or more parathyroids lie on the anterior surface of the gland. In 30%, one or more parathyroids are present on the lateral surfaces of the gland. The clinical significance of this work is self-evident. With modified technic, leaving the lateral and part of the anterior capsule of the thyroid, approximately two-thirds of the parathyroids now removed are saved. Parathyroids may be recognized at operation by their characteristic appearance and reimplanted.

Histologic studies on endocrines of chickens deprived of ultraviolet light. I. Parathyroids. Nonidez (J. F.) & Goodale (H. D.), *Am. J. Anat. (Phila.)*, 1927, **38**, 319; *Abst. J. Am. M. Ass.*, **88**, 1031.

Nonidez and Goodale noted that the combined effect of lack of direct sunlight and a ration poor in antirachitic vitamin on the parathyroids of growing chicks is expressed in enlargement of these glands. Microscopic examination of the glands show that this enlargement is due to increase in cell size (hypertrophy), and increase in number of the epithelial cells (hyperplasia). The phase of hypertrophy and hyperplasia is followed by a phase of regression during which the epithelial cords appear shrunken. Shrinkage of the cords may coincide with hyperplasia of the stroma. Local degenerative changes, such as production of keratin and mucous degeneration, were present in the regressed glands of some of the chickens examined. It is suggested that these phenomena are not the immediate result of the treatment, but are caused by some other factors of unknown nature, and that degenerative tendencies are probably favored by the abnormal condition of the glands. The parathyroids of chickens that are deprived of ultraviolet rays for five weeks and subsequently exposed to direct sunlight are much smaller than the corresponding organs in younger birds not receiving exposure. Microscopic examinations show that the decrease in volume of the glands is due to a decrease in cell size, resulting in considerable crowding of the epithelial cells. Pressure atrophy also occurs in some of the glands.

Goiter prevention. McCarrison (R.), *Brit. M. J. (Lond)*, 1927, **1**, 94; *Abst. J. Am. M. Ass.*, **88**, 1037.

McCarrison gives additional evidence bearing on the importance of providing a chemically and bacteriologically pure water supply, if goiter is to be eradicated. Iodine, he says, has nothing to do with the matter. Goiter, which had been endemic in Sanawar for seventy years, has now disappeared; and its disappearance has been due to the introduction of a new and protected water supply. Its eradication within the short space of three years is, McCarrison says, unparalleled in the history of goiter prophylaxis.

Changes in the thymus and thyroid in endemic goiter. Messerli (F. M.) & Coulaud (E.), *Ann. de l'Inst. Pasteur (Par.)*, 1926, **40**, 952; *Abst. J. Am. M. Ass.*, **88**, 1039.

Messerli and Coulaud's research was conducted on rats. In Paris, where endemic goiter does not exist, the size of the animals' thyroid was half that of rats in Strasbourg and Lausanne, where a few cases of endemic goiter are observed. In Zurich, where endemic goiter is frequent, the thyroid of the animals was three or four

times as large as that of rats in Paris. In all instances, the volume of the thymus paralleled that of the thyroid. This accords with Wagner von Jauregg's report that thymus extracts associated with thyroid extracts are effectual in preventive treatment of endemic goiter and of cretinism. It is probable that in countries with endemic goiter the thymus persists longer in man.

Treatment of obstinate obesity. Shepardson (H. C.) & Allen (R. E.), California and Western Medicine (San Francisco), 1927, 26, 33.

In two cases of obesity the basal metabolism, as determined by the ordinary methods, was within normal limits, yet it was apparent that the actual metabolism was decidedly abnormal. In each instance the diet was reduced to a level considerably below the basal requirement without impairment of health, and a definite loss of weight resulted beyond which further reduction was unobtainable by dietary restriction alone. Thyroid extract was then used, as a general stimulant to metabolism rather than to supplement a thyroid deficiency, which neither of these cases showed. This addition of the thyroid extract resulted in further loss of weight and permitted an increase in the diet to a point where moderate exercise produced no untoward effect, such as might have been produced on the previous extremely low caloric intake. This form of treatment is not advocated in all cases of obesity. It was employed in the study of more difficult cases only when they could be kept under close observation. The grave danger of any form of reduction régime which produces a too rapid loss of weight is emphasized.—M. O. Lee.

The course of hyperthyroidism under iodine medication. Starr (P.), Arch. Int. Med. (Chicago), 1927, 39, 520-535.

The course of hyperthyroidism under iodine medication is characterized by remission and recurrence during the administration of iodine and by a reaction, which may be extreme, after the iodine is discontinued; hence, the prolonged treatment of patients who have hyperthyroidism with iodine in dosage sufficient to produce these effects is without final benefit.—Author's Abst.

Endocrinology

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STUDIES ON THYROIDS*

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The results of four rather unusual kinds of study on the thyroid supply the basis for this discussion. Our studies have been made on doves and pigeons. These animals are peculiarly adapted to thyroid studies, since they feed exclusively upon the same dry grains throughout the year, and from them the complete reproductive history of all individuals is readily obtained.

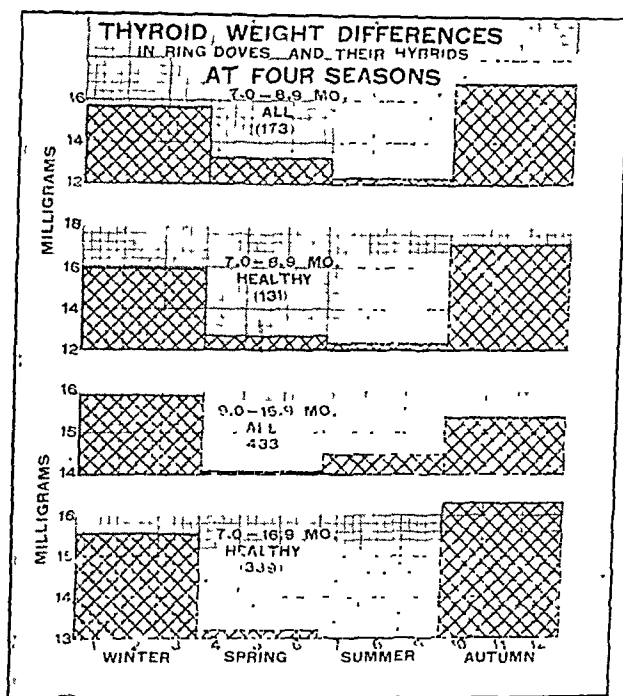
SEASONAL VARIATIONS OF THYROID SIZE

The data obtained by Riddle and Fisher (1925) show that in three kinds of pigeons the thyroid notably and promptly enlarges in autumn and winter and becomes smallest in summer; a decrease in size begins promptly with the appearance of warmer external temperature in the early months of spring. It was shown in the paper cited that this result was obtained on material practically free from the complicating effects of diet, care, locality, race, age, length or degree of confinement, health, and body size of the animals examined.

The polygons of Figure 1, and that at the bottom of Figure 2, provide some hitherto unpublished data on the nature and extent of this seasonal change. Only seasonal *differences* are

* Read at the Eleventh Annual Meeting of the Association for the Study of Internal Secretions, Washington, May 17, 1927.

plotted on these polygons, but the values (abscissae) given provide exact information on the average size of the thyroids at each of the four seasons. The three months composing each season are of course here thrown together. Some irregularities in the seasonal averages may appear when, in addition to healthy birds, those infected with round worms (ascariasis) are also included in the averages (second polygon from bottom of Figure 1).



Though the animals which supplied these data were given considerable protection from cold, they were subjected to lower temperatures during the autumn and winter than during the remainder of the year. The common pigeons were kept in separate buildings from the ring doves and were supplied with less heat. Our data show a more pronounced seasonal change in the thyroids of common pigeons than in those of the ring doves.

The thyroids of doves and pigeons were found to increase with age. Only in birds older than 30 months was any sexual difference in thyroid size observable in our data—the average size of the female thyroids thereafter was somewhat larger. In diseased birds the thyroid size was more variable than in the

healthy. This study was based on careful weighings of 890 pairs (the pigeon thyroid is a paired organ) of thyroids. The histology of a few "winter" and a few "summer" thyroids have been examined. The winter thyroids show the more active and the summer thyroids the less active condition.

These results are free from certain objections which must be raised concerning the available data for seasonal thyroid change in mammals and man. Nevertheless the present and earlier data are in substantial accord.

In animals killed in an abattoir Seidell and Fenger (1913, 1914) found that the weights of fresh glands, as well as their iodine content, show a more or less regular seasonal change in cattle and sheep. Low and high iodine content were observed to correspond to winter and summer, respectively; but the size of the glands was more loosely correlated with winter and summer—due doubtless to the heterogeneous and largely unknown nature (age, size and source) of the animals supplying the thyroids. Herzfeld and Klinger (1922) have stated that data obtained by them on the thyroids of human (Swiss) subjects suggest an enlargement of this gland in winter. They also obtained higher percentages of iodine in summer, lower in winter; their data, however, are rather meager and by no means cover the various parts of the year.

In addition to the above data specifically based on season, the literature contains some observations on changes of size and histological appearance in the thyroids of animals subjected to periods of heat or cold. In rats kept on a controlled diet and exposed to cold during several days Cramer (1916) observed histological changes which are probably similar to those observable in "winter" thyroids of other animals. Mills (1918) likewise found both directions of change in the thyroids of rabbits, cats and guinea pigs subjected to heat or to cold during one to four weeks. Hart (1922) subjected a group of gray mice to heat, and others to cold, during a few weeks. A reduction of thyroid size was observed in the former group and evidence of increased function in the latter group. When individuals of either group were restored to normal temperatures, it is stated that their thyroids soon regained their normal size and histological appearance. Finally, Adler (1920) observed that races of the grass frog (*Rana temporaria*) from higher

and colder (Alpine) regions have larger thyroids than those from warmer (Adriatic) regions; while those from an intermediate altitude and climate (Bavaria) have thyroids of intermediate size. In experimental cultures of tadpoles he also found atrophic thyroids in animals raised at high temperatures, while hyperplastic thyroids were found in those raised at low temperatures. On the other hand, it was elsewhere reported that in hibernating hedgehogs the size of the thyroid is decreased.

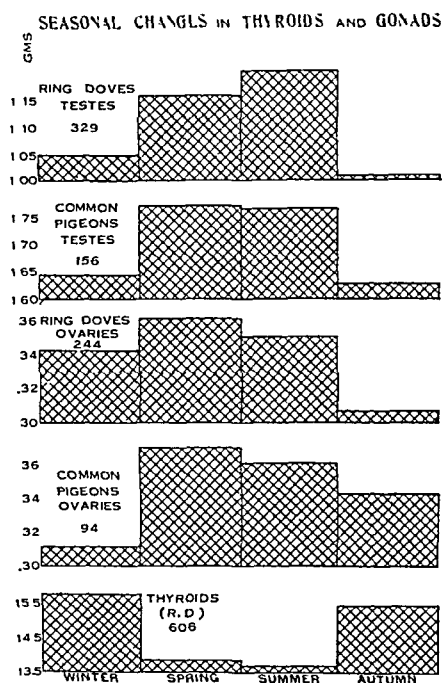
The facts now available unmistakably lead to the conclusion that the thyroids of non-hibernating higher vertebrates normally undergo enlargement in autumn and winter and become smaller during spring and summer; that these size changes are responses to the external temperature; and that the enlargement from this cause is accompanied by an increase of hormone-production in this organ.

In the application of these findings to normal and abnormal conditions of the thyroid in man various facts and observations will become uppermost in the thought of different investigators and clinicians. It is our wish further to note only that in primitive man, as in higher vertebrates generally, this seasonal rhythm of thyroid size and function was probably in full swing; and that—as shown in the next section—thyroid rhythm seems initially to bear a relation to gonad and reproductive rhythm. But civilized man in temperate and cold climates has probably partially defeated this primitive rhythm by wearing more clothing in winter, by building homes, and by supplying heat to these homes. Are there results or consequences of this repressed rhythm of thyroid function?

RECIPROCAL SIZE CHANGES OF GONADS AND THYROIDS IN RELATION TO SEASON

We may now examine the seasonal changes in gonad size in practically the same groups of birds which supplied the data just examined for thyroid size. When the two series of measurements are thus compared it is found that the periods (autumn and winter) of increased thyroid size are periods of decreased gonad size. On the other hand, the seasons (spring and summer) of reduced thyroid size are seasons of gonad enlargement. It is further found that the period of free or frequent ovulation in these same pigeons coincides with the

period of diminished thyroid size and of larger gonad size; the period of restricted ovulation—and also of more frequent reduction of the pigeon's clutch to a "single" egg—coincides with the period of increased thyroid and decreased gonad size. In Figure 2 are shown some hitherto unpublished data which establish these relationships. Other data will be found in an earlier study (Riddle, 1925).



From an inspection of these data it would at first seem obvious that the alternating or reversed seasonal changes in thyroid and gonad indicate antagonistic relationships between these two glands. Unless accompanied by certain reservations, however, such a conclusion does not seem necessary. The reasons are: First, in birds we are able at many points to distinguish sharply between *sex* and *reproduction*. And there is evidence that both thyroids and gonads in birds are intimately related to both sex and reproduction. Second, whatever may be said of single or multifarious functions of the thyroid, the gonad is both a reproductive and a sexual organ; and it is only a coincidence of increased thyroid activity with a diminution or suppression of an aspect of *reproduction* that is indicated by

our results. Third, other studies made in our laboratory make it seem probable that the antagonism involved in this repressed reproduction lies between the thyroid and suprarenal rather than directly between the thyroid and gonad. This point can not be discussed here. Fourth, some evidence at hand indicates that abnormally *small* thyroids as well as abnormally large ones are accompanied by decreased reproduction in (female) pigeons.

Nevertheless our data make it clear that size rhythms in thyroid and gonad do alternate in pigeons, and that the alternating periods of large size mean, in both these organs, periods of increase in an easily definable function. The season of largest thyroid size is its period of most active hormone production; and during this period the gonad—testis or ovary—is smallest and least active in its reproductive function. In summer these states are reversed. Common pigeons may reproduce during a dozen years, and it is practically certain that twice annually throughout this period the thyroid and gonad thus rhythmically and alternately increase their size and function.

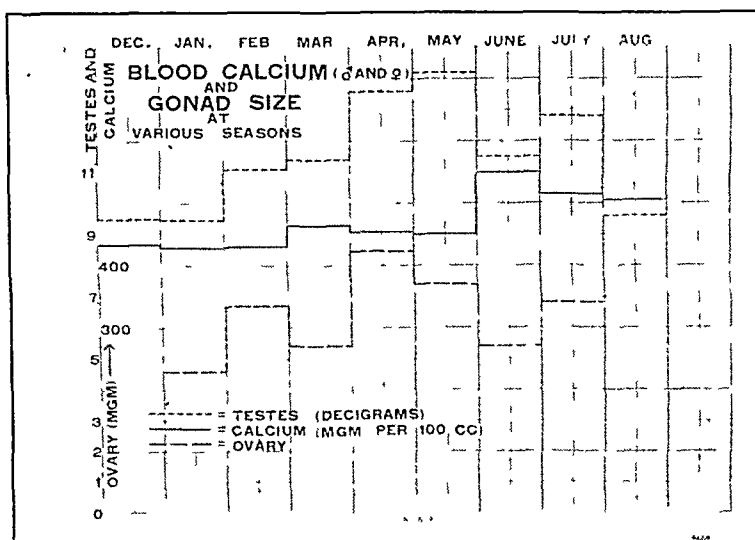
That this relationship of thyroid and gonad is not a chance or fortuitous one in these animals is made clear by many facts that could be cited. That a similar relationship extends beyond the two species belonging to two zoological families (*Columbidae*, *Peristeridae*) in which the point has been adequately investigated is perhaps a matter that will be conceded by all. Whether this simple relationship applies to man is yet to be investigated. The fact inviting such investigation is, however, at hand.

SEASONAL VARIATIONS IN PARATHYROID ACTIVITY (SERUM CALCIUM) IN RELATION TO THYROID AND GONAD

To whatever extent the level of the serum calcium may indicate parathyroid activity we are also able to examine the question of seasonal changes in the parathyroid. Moreover, since the weights of the thyroids and gonads were at once obtained on the same individuals which supplied the data for blood calcium, it is possible to plot the size of these organs against the calcium values. Unfortunately, the available data do not represent numbers large enough to make it certain that the curves tell an entirely true story. These data were obtained rather incidentally to a more serious investigation of blood cal-

cium changes in the reproductive cycle (Riddle and Reinhart, 1926).

The relation of season to the blood calcium of healthy adult ring doves of both sexes is shown in Figure 3. The values are plotted by months. One finds a fairly distinct increase of blood calcium in spring and summer over the values obtained in winter. On the same figure we have plotted the weights of the thyroids of the particular birds which supplied the calcium values in the various months of the year. It will be seen that these particular thyroids tend to become smaller during those months (June excepted) characterized by increased calcium

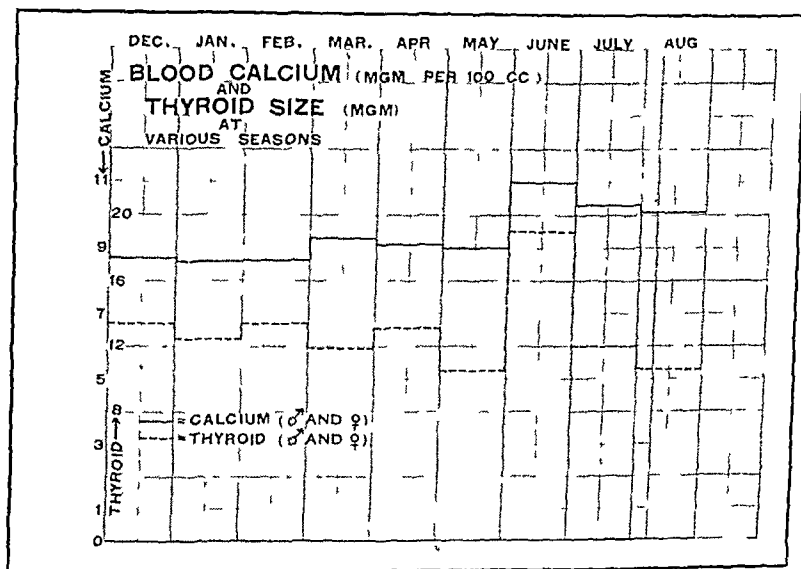


values. Only 55 thyroids are included in this curve, but reference to the more extensive data on this subject—already discussed at the beginning of this paper—will show that this curve for thyroid size accurately represents (apart from the exceptional status of June) the normal seasonal change in the thyroids of pigeons. The data of Figure 3 indicate that the season of apparent high blood calcium in pigeons is certainly the season of low thyroid size, and *vice versa*.

In Figure 4 the curve for seasonal change in blood calcium is again reproduced, and the size of the ovaries and testes of the particular birds which supplied the calcium data are plotted against the calcium curve. Here it will be observed that periods of low blood calcium coincide with periods of smaller size

in ovary and in testis. Although the data given here for testis and ovary are rather inadequate, because of limited numbers and the considerable size variability in these organs, an adequate amount of earlier evidence—also discussed above—shows that the seasonal change of ovary and testis which is indicated here is typical and normal.

Our evidence for a seasonal change of the blood calcium level is somewhat strengthened by two earlier observations that have been made on seasonal change in blood phosphates and in the size of the parathyroids. The value of the seasonal change in phosphates as evidence on our present topic lies in the cir-



cumstance that in healthy individuals blood phosphorus and blood calcium usually tend to change in the same direction. Hess and Lundagen (1922) found in the blood of infants a low percentage of phosphorus in winter and a high percentage in summer; and this effect is attributed mainly to the seasonal variations of sunlight. This is precisely the relationship that we find for season and calcium. Still more closely identified with the present topic are the results obtained on rabbits by Grant and Gates (1924), who noted a marked diminution of size in the parathyroids between November and February. Further, treatment of the animals with ultra-violet light produced more notable size changes in the parathyroids than in other

organs—the parathyroids becoming markedly enlarged. Grant and Gates (1925) also carefully studied the blood calcium of the treated and untreated rabbits, but an effect of caging or confinement was found which served to complicate their data for seasonal change. These investigators have hesitated to draw a conclusion as to a seasonal change of blood calcium, and emphasize rather that “a parathyroid hypertrophy of 20 to 50 per cent does not result in a corresponding increase in the calcium content of the blood when the concentration is already at or near the normal level.” They find that in general the blood calcium and phosphorus tend to change in the same direction.

Evidence for a seasonal change in the level of blood calcium is thus found in our own data and in the data of other workers. In immature pigeons lower values were found in winter and higher values in summer. In the pigeon it is known that the testes and ovaries undergo a size change in the same direction as the serum calcium, and that the thyroid is largest at the time the serum calcium is at its minimal seasonal value.

THE ESTABLISHMENT OF RACES OF PIGEONS WITH CHARACTERIS-
TICALLY LARGE AND WITH CHARACTERISTICALLY
SMALL THYROIDS

A fourth, and very important line of study has been concerned with the establishment of races or strains characterized by large or by small thyroid size. This investigation must be fully described elsewhere (probably in the *American Naturalist*), and only a short statement concerning the main result can be given here.

At the outset we had a rich variety of material, both in common pigeons and in ring doves, from which to undertake this study. Numerous individuals with normal and others with various types of abnormal reproductive performance were at hand. Two years of previous study had led to the conclusion that these various types of reproductive disturbances were ascribable to neither nutritional deficiency nor to infection. These exclusions directed attention to their probable origin in endocrine disorder. It was therefore decided, now nearly six years ago, to learn what had already unintentionally been done, or could later purposefully be done, toward establishing definite “thyroid” races in these mongrelized birds—races permanently characterized by large or small thyroid glands.

It must be said that it is still too early to evaluate the relative importance of the earlier breeding history as compared with the definitely directed procedures of the past five years; and we further realize that the whole subject is much complicated and that thus far we have only imperfect knowledge of the sources of temporary, as distinct from hereditary, thyroid-size variations. Nevertheless, it is evident that we now have "large thyroid" races and "small thyroid" races of ring doves. For individuals belonging to one of these strains or races it is

TABLE I
ESTABLISHMENT OF "THYROID RACES" IN RING DOVES

	Race	Generation	Parents and Offspring	No.	Group Averages		
					Age (mo.)	Body Weight (grams)	Thyroids mgms.
With LARGE thyroids	162	F ₁	Parents.....	2	62.1	174	22.7
			Offspring.....	16	14.2	166	20.3
		F ₂	Parents.....	9	16.7	170	20.9
			Offspring.....	28	11.7	158	20.9
		F ₃	Parents.....	4	16.9	165	27.4
			Offspring.....	14	17.8	159	24.7
		F ₄	Parents.....	2	26.7	152	25.5
			Offspring.....	4	11.1	157	25.0
	311	F ₁	Parents.....	2	22.0	(165)	38.3
			Offspring.....	10	15.9	160	20.3
		F ₂	Parents.....	8	16.4	159	18.4
			Offspring.....	15	14.9	152	19.2
		F ₃	Parents.....	6	19.1	148	16.8
			Offspring.....	8	12.3	147	17.4
		F ₄	Forced to continue race three-fourths pure 311.		by crossing	F ₃ with out-cross only	
With SMALL thyroids	36	F ₁	Parents.....	2	89.8	165	15.0
			Offspring.....	5	16.0	158	12.9
		F ₂	Parents.....	2	18.0	160	12.1
			Offspring.....	15	13.0	159	11.1
		F ₃	Parents.....	6	17.9	157	11.6
			Offspring.....	21	10.9	146	13.0
		F ₄	Parents.....	2	20.0	174	11.8
			Offspring.....	1	13.8	140	12.1
	161	F ₁	Parents.....	2	50.8	186	15.0
			Offspring.....	31	17.7	171	13.8
		F ₂	Parents.....	4	19.8	167	11.0
			Offspring.....	10	21.3	166	12.5
		F ₃	Parents.....	4	25.0	171	13.0
			Offspring.....	9	16.2	(165)	12.1
		F ₄	Parents.....	2	30.6	160	11.0
			Offspring.....	2	10.6	160	11.1

now possible—on the basis of pedigree only—to predict the presence of thyroids larger or smaller than normal.

Summaries for four such races are given in Table 1. Two strains or races of ring doves with large thyroid size, and at least two races with small thyroid size, appear to have been established. Through four successive generations a great majority of the healthy individuals of these races have shown thyroids characteristically large or small in accord with their race. We have fifteen or twenty ring dove races whose thyroids are of intermediate size.

Concerning the interest and importance attaching to this result it may be noted that this is the first time that a race characterized by the size of an endocrine organ has been obtained in genetical study. It is further notable that in many respects human races and nationalities are the genetic or biological equivalents of the races upon which our studies have been made. The possibilities of the establishment of races or strains of one or another thyroid size are, theoretically, similar in the two forms; the advantages, perils and disadvantages to a race of an hereditarily large or small thyroid are already susceptible of examination in these races of pigeons. Such studies are already being made. We now make no statement as to whether the large thyroids exhibit hyper- or hypo-function. Our laboratory, in collaboration with Professor F. G. Benedict, will soon resolve this question by studies now in progress on the basal metabolism of these "thyroid" races.

SUMMARY

The thyroids of various species of pigeons undergo a functional enlargement during the autumn and winter months and a progressive decrease in size during the months of spring and summer. These changes follow as prompt responses to the external temperature.

In various kinds of doves and pigeons both testes and ovaries enlarge during the spring and summer, and decrease in size during the autumn and winter. This is precisely the reverse of the seasonal size changes in the thyroids of these same animals.

If seasonal changes in the serum calcium level represent changes in parathyroid activity this organ is probably more active during spring and summer than during winter. Great-

est parathyroid activity thus coincides with greatest gonad activity and with lowest thyroid function.

Races of doves characterized by large thyroid size, and other races characterized by small thyroid size, have been successfully established.

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HOW FAR CAN RECENT STUDIES ON THE OVARIAN FOLLICULAR SUBSTANCE BE APPLIED TO THE HUMAN? A BRIEF DISCUSSION OF THE THERAPEUTIC ASPECTS OF THE PROBLEM*

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BALTIMORE, MD.

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In 1923 Loeb made the statement that "while the evidence concerning the maturing follicles as the cause of the changes in the first phase of the sexual cycle is not as definite as the evidence relating to the significance of the corpus luteum in the second phase, still, as it stands at present, the evidence points very strongly to the conclusion that the maturing follicles or the follicles nearing the stage of maturation dominate the first phase in the same way as the corpus luteum dominates the second phase." The interesting series of studies published during the past few years seem to have almost completely reversed the view enunciated by Loeb, for certainly the recent trend has been to stress the role of the follicular fluid and to minimize that of the corpus luteum.

The purpose of this communication is merely to set forth the reaction to these recent studies of one who has been more particularly interested in the study of the human reproductive cycle. The deep interest of gynecologists and obstetricians in the laboratory study of the sexual cycle in the lower animals is easy to understand, when one considers the difficulties of the experimental approach in the study of menstruation in women. The fact that our friends the anatomists and physiologists have taken such vigorous hold of this problem bodes well for far more rapid progress along this line than would otherwise be possible.

At the outset I may say that the views of Loeb on the relative importance of the follicles and the corpus luteum harmonize much more readily with what we know of the human problem than do those of Allen and his co-workers, Frank and others,

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important and accurate as these studies no doubt have been. It has seemed to me that, in applying animal results to the human problem, too little cognizance has been taken of the important differences between the sexual cycles of the lower animals and the human female. In many of the lower animals, such as the rat, the cycle is unquestionably dominated by the follicle. Oestrous phenomena are readily produced in spayed animals (Allen and Doisy) or those which are immature (Frank and others) by the injection of follicular fluid. But these phenomena are not easily comparable with those observed in the human female, from either an anatomical or a physiological standpoint.

To bring out this fact, let us for a moment review the conception of menstruation which has come to be quite generally accepted by gynecologists and obstetricians. This conception, I may add, is not by any means speculative, nor does it represent a blind acceptance of the views enunciated by Fraenkel in 1903 as to the importance of the corpus luteum in the physiology of the process. It is based chiefly upon careful histological and clinical correlation of the ovarian and endometrial cycles. It is to this method of study, for example, that we owe our newer knowledge of the time of ovulation, which is now accepted as occurring, *not at the time of menstruation*, as was formerly believed, but at approximately the thirteenth or fourteenth day of the cycle, with considerable individual variation in different women.

The ovum, after its discharge from the follicle, begins its passage down the Fallopian tube, this requiring several days at least. In the meantime the endometrium is making preparations for its reception. In the immediately post-menstrual phase the endometrium is thin, but it undergoes a steady development from day to day, probably under the influence of the maturing follicles, for the old corpus luteum is now definitely retrogressive, and the new one is in its early formative phase. The glands, at first narrow and collapsed, increase in width and tortuosity, this continuing throughout the long interval phase up to a period of four or five days before the next menstrual hemorrhage. During this time the corpus luteum is steadily developing, reaching its mature phase four or five days before the period, and its histological appearance, at least, suggests a definite incretory function.

It is during this phase of the corpus luteum that we find a picture in the endometrium which can scarcely be construed as a mere advance on the preceding slow hypertrophy, for an entirely new feature is added. For the first time the glandular epithelium presents striking evidence of secretory activity, be-

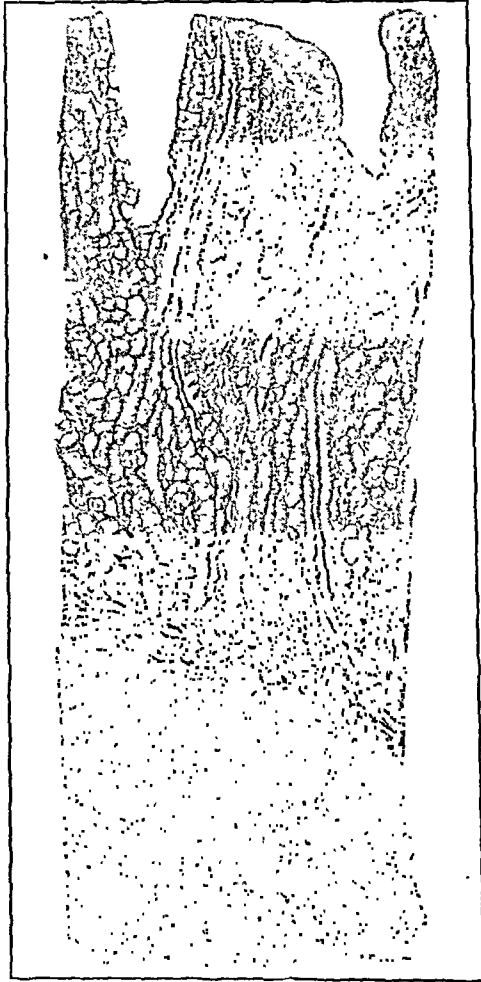


Fig. 1. Typical human premenstrual endometrium, with which one characteristically finds (I have encountered no exception) a mature corpus luteum in the ovary. Note secretory change in gland epithelium.

coming low and frayed, the cells often melting away into a mucoid secretion within the lumen. This characteristic is so striking that it can be recognized at a glance, and this phase is, indeed, commonly alluded to as the secretory phase (Fig. 1).

So far as I have been able to gather, such a picture is not encountered in the laboratory animals where sexual cycles have been recently so extensively studied. This statement will apply, I believe, to both the normal oestrous cycle and those produced artificially by injections of follicular fluid.

Certainly the photographic representations of the endometriums of monkeys in these phases, as given by Allen, bear no resemblance to the premenstrual endometrium of the human. Indeed, the only exception to this general statement is to be found in one of the cases pictured by Corner in a forthcoming paper, which he has kindly placed at my disposal (Fig. 2). In this case the histological picture can not be distinguished from

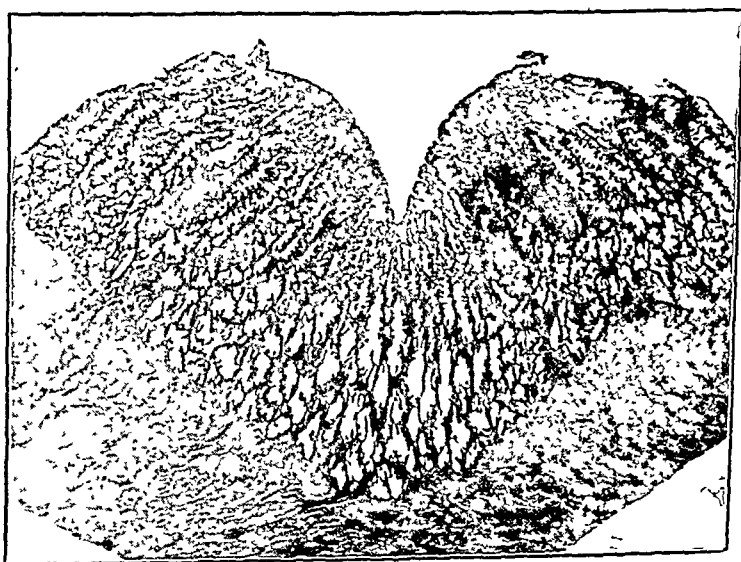


Fig. 2. Premenstrual endometrium in monkey, associated in this case with the mature corpus luteum in the ovary, as in human. This picture is exactly like that found characteristically in the human (see Fig. 1), although this type of premenstrual change appears to be less common in the monkey than that shown in Fig. 3. For this picture I am indebted to Dr. George W. Corner.

that characterizing the premenstrual endometrium in the human. The significance of this will be discussed later in this paper.

Does not this common lack of the secretory phase in the lower animals suggest that the corpus luteum is the factor responsible for this topping-off of the endometrial development, rather than the growing follicle, which now, indeed, is almost at its ebb? In other words, at the time when the endometrial changes reach their acme the development of the follicles is far

less advanced than it is just before ovulation, which takes place about two weeks later. And yet, just before ovulation, when the follicle is fully mature, the development of the endometrium is at a relatively low ebb. I am aware, of course, that other follicles than the dominating one of that particular cycle may conceivably be concerned in the premenstrual hypertrophy, but to assume that their influence at times overshadows that of the presiding follicle and at other times is subordinated to it presupposes an interfollicular antagonism which appears highly illogical, and, so far as I know, has no scientific support.

On the basis of observations upon laboratory animals, the current trend appears to be to doubt that ovulation is a necessary precursor of menstruation. This skepticism has much to support it in the case of the lower animals, but very little in the case of the human being. Especially' interesting, in this connection, has been the study made by Corner of the sexual cycle in monkeys, in which there occurs a menstrual cycle readily comparable with the human process. In his study of a series of monkeys (*Macacus rhesus*), in 1923, Corner found that in a considerable proportion no corpus luteum was to be found in the ovaries when these were removed immediately after what was apparently a genuine menstrual flow, and he therefore very properly questioned whether the corpus luteum plays any part in the process.

As far back as 1906 van Hewerden, in the autopsy study of a rather large series of monkeys, made the same observation. From this standpoint this author divided the animals into two groups. In one the uterine mucosa shows marked premenstrual swelling; with striking tortuosity of the glands, and definite secretory characteristics. In all the animals of this group prominent follicles or well developed corpora lutea were found in the ovaries. In the other group, the endometrium was thin, and the premenstrual swelling much less noticeable, while the glands showed none of the cork-screw tortuosity found in the other group. Furthermore, corpora lutea were not seen in the ovaries.

Corner's paper, in which he suggested the possibility of menstruation without preceding ovulation, has been answered by Robert Meyer, who pointed out, among other things, that it was difficult to be sure that the bleeding observed in Corner's

monkeys was in all cases analogous with normal menstruation. In the human female we likewise not infrequently encounter a form of pseudo-menstrual bleeding in which corpora lutea are not only absent, but characteristically so. This form of abnormal menstruation is very common in women near the menopausal epoch, but may occur at any age during the reproductive years. It is not rare at or near the time of puberty.

As already mentioned, the characteristic findings in the ovaries of such cases are an absence of corpora lutea, and the presence of a persistent unruptured follicle, or, perhaps, of many maturing follicles. I believe that in such cases we are actually dealing with a follicular type of cycle, which persists in a vestigial way in certain individuals.

But this is certainly not the usual process observed in human females. Every gynecological pathologist will discredit this assumption. The examination of thousands of ovaries, in correlation with the endometrial changes and the menstrual histories, has convinced me of the regularity and normality of our findings in this respect. Just after menstruation we expect to find, and do find, the characteristic undeveloped endometrium (post-menstrual type) and, in the ovary, a retrogressing corpus luteum; in the interval phase we find a slowly developing hypertrophy of the endometrium, and, in the ovary, a corpus luteum showing more advanced retrogression. Moreover, it is in this stage that we find the earliest stage of the new corpus luteum resulting from the rupture of the mature graafian follicle. Again, in the few days just before the next menstrual period we confidently expect to see the pregravid or secretory endometrium above described, and, in the ovary, a typical mature yellow body. Finally, the period of menstrual casting off of endometrium is accompanied by beginning retrogression of the corpus luteum. These observations have been made in so many laboratories by so many men that they must be accepted as authoritative evidence, just as we accept the quite different results obtained in the lower animals by the anatomists and physiologists.

For certainly this histological cycle does present important differences from that seen, for example, in the rat, in which the cycle is apparently fully run under the influence of the follicle alone, and in which it can be reproduced, in the spayed

animal, by injection of follicle fluid alone. The relatively infrequent form of uterine bleeding above alluded to, in which corpora lutea are absent, constitutes the exception and not the rule. This type of menstruation is characterized especially by its excessiveness (functional menorrhagia), and this is presumably due to the absence of the corpus luteum, which normally exerts an inhibitory effect upon the further maturation of follicles.

It is possible that, in rare instances, even a normal menstrual flow in the human may occur without ovulation; that is, that it

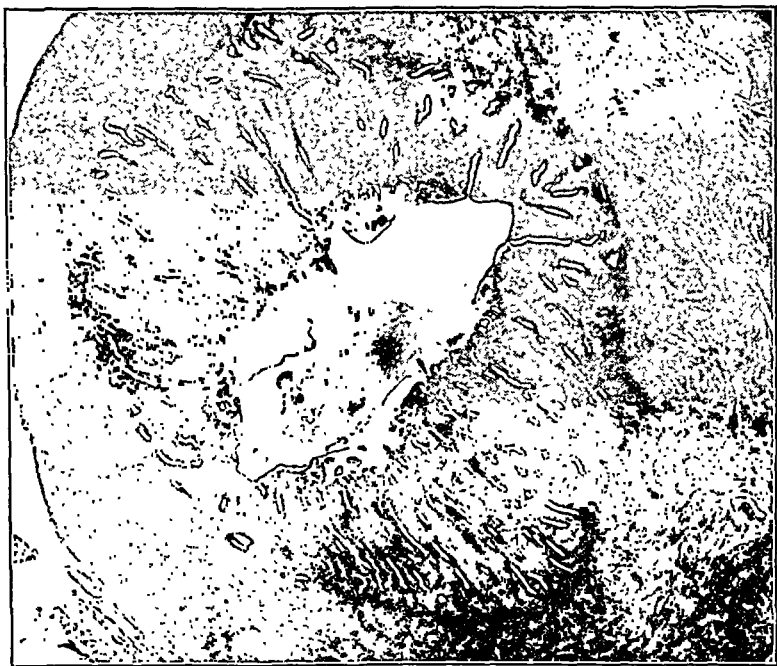


Fig. 3. Type of endometrium found just after onset of menstrual bleeding in monkey, with no corpus luteum in the ovary, but, instead, a mature Graafian follicle. This association appears to be more common in monkeys than the corpus luteum type, shown in Fig. 2. For this picture I am indebted to Dr. Carl Hartman.

may be due to the influence of the follicle alone. Until recently such a view would have seemed untenable to me, and even now I know of very little direct evidence to support it. But the splendid researches of Corner, Allen and Hartman upon monkeys, and the knowledge that in the human being a form of uterine bleeding, often definitely periodic, may be due to follicular influ-

ence in the absence of corpora lutea, makes it difficult to deny the possibility above alluded to.

Much light is thrown upon this problem by a study of the endometrium just before menstruation in monkeys. As already mentioned, Allen's illustrations show no such condition as we find in the human at this phase. Corner also emphasized this fact, and, in his forthcoming paper, speaks of two different kinds of premenstrual endometrium. One is essentially similar to the human and follows ovulation by about twelve or fourteen days. The other is devoid of the premenstrual features seen in the human, and apparently is not dependent upon a preceding ovulation. The latter is the more frequent type in monkeys, but the menstrual bleeding in the two groups of cases is apparently indistinguishable in type. The second type, which we may for convenience allude to as the follicular type, is well illustrated in Fig. 3, for which I am indebted to Dr. Hartman. This endometrium was obtained from a monkey just after the onset of menstrual bleeding. A large follicle was found in the ovary, but no corpus luteum.

Knowing the accuracy of these observations of Corner and of Hartman, the conclusion seems inescapable that in the monkey either one of two types of cycle may occur. One is dependent upon ovulation, and in this the corpus luteum plays an important role, part of which at least is the production of a pre-gravid endometrium similar to that seen in the woman. In the second type, ovulation is apparently not essential, and in this the corpus luteum plays no known part, while the endometrium fails to show the markedly hypertrophic and secretory changes characteristic of the human premenstrual phase.

As already mentioned, there can be no doubt that in the human female the prevailing mechanism of menstruation is of the first of the two types above mentioned, *i. e.*, the corpus luteum type, as it may be spoken of for convenience. The evidence for this seems overwhelming. There are, it is true, a few scattered observations in the literature tending to show that menstruation may occur without ovulation and corpus luteum formation. Most of these, however, are unconvincing. And yet, as already stated, it would be strange if the follicular type of menstrual cycle did not occasionally persist in the human species. A recent observation of my own is suggestive, though not conclu-

sive. A young woman of 19 whom I had treated for two years for functional menorrhagia was taken with acute appendicitis, so that an opportunity was given to inspect at least hastily the ovaries, as a right rectus incision was employed. I may add that, whereas her periods had formerly lasted for as much as two or three weeks and had been very profuse, the two or three periods immediately preceding the operation were much more moderate, lasting only four or five days. There had been no flow for two months until the day before the operation, when a slight menstrual show appeared. At operation the right ovary presented a large translucent follicle, evidently mature. No sign of a corpus luteum could be seen in this ovary nor in the left. The day following the operation menstrual bleeding was resumed quite freely. This case suggests that the responsible factor was the large mature unruptured follicle, as, in my experience, a mature corpus luteum can usually be detected even by simple inspection of the ovarian surface. Certainly none could be found in this case. This is the only instance which I have personally observed which would shake my belief in the invariability of the rule that menstruation cannot occur without a corpus luteum, *i. e.* without a preceding ovulation. I believe, however, that more careful observation may conceivably show such cases to be less rare than I now believe them to be.

It would hardly seem necessary here to dispel a superficial misconception held by some of our profession to the effect that the corpus luteum is responsible for menstruation, applying the latter term to the actual bleeding of the process. This structure, of course, has nothing to do with the direct causation of the menstrual discharge itself. Indeed, menstrual bleeding occurs not because of, but in spite of, the corpus luteum influence. The latter, we believe, is responsible for the final and characteristic secretory developmental phase. If the corpus luteum influence persists undisturbed, as when pregnancy supervenes, the endometrial hypertrophy advances still further to genuine decidual formation. But if the corpus luteum influence is checked, as it is when fertilization fails and the ovum of the preceding ovulation reaches the end of its life span, then its protective influence over the growing endometrium is removed and the endometrium dismantles itself, with bleeding as a chief accompaniment.

These statements are here set forth rather baldly, but they are supported by much evidence, except for the assumed influence of the ovum itself. We have no way of determining this point, and yet, a cell with such amazing potentialities as the ovum may well exert profound influences even before fertilization. How else can we explain the remarkable periodicity of the menstrual phenomenon than by ascribing it to some innate quality of the germ cell itself?

The above conception of menstruation and of the role of the corpus luteum is borne out by certain observations which can be made in the gynecological operating room. I have often noted that if, in a woman operated upon several days before the expected onset of menstruation, it becomes necessary to remove the ovary containing the corpus luteum, menstruation is precipitated, *i. e.* it occurs soon after the operation, often within a matter of twelve to twenty-four hours, and rarely later than forty-eight hours. As far back as 1911 Neu made somewhat similar observations, although he did not correlate them with the corpus luteum, which was just becoming an object of intensive study.

The explanation of such an anticipation of the normal menstrual date would seem to be in the removal of the corpus luteum influence, just as it normally is checked by the death of the ovum, if this be actually the dominating factor. It is, of course, conceivable that the premature onset of menstruation in such cases may be due to the nervous shock of the operation. This can be readily controlled by studying the effect upon menstruation of pelvic operations in which the corpus luteum is not disturbed. I have done this systematically only since beginning the preparation of this paper, but the small series of observations thus made, together with the general impressions gained over many years before this, makes me feel very strongly that it is the corpus luteum factor which is concerned with this disturbance of menstrual rhythm.

There are one or two discordant observations noted in the studies of those who consider the follicle the dominating factor in the menstrual cycle. For example, Allen, in a forthcoming complete study of the cycle in monkeys, which he has generously allowed me to read in manuscript form, states that "reddening of the skin of the vulva and surrounding regions, the

'sexual skin,' was usually present to some degree during the whole menstrual cycle. It often became intense during the interval." Dr. Carl Hartman, of the Carnegie Institute of Embryology, who is now studying the reproductive cycle in a considerable colony of monkeys, makes the same observation, and has very generously demonstrated to me this and many other aspects of the problem. But this deepening of the sexual skin is presumably due to the increasing intensity of the follicle influence, which reaches its acme just before ovulation, *i. e.* at about the thirteenth or fourteenth day of the cycle. Does it seem probable that this same follicle influence which now begins to wane, if one may judge by the sexual skin change, would nevertheless be responsible for the endometrial hypertrophy, which now for the first time begins to become pronounced. At menstruation, it may be added, the sexual skin fades, so that the hue is lighter than at any other period in the cycle.

It is of interest to note, also, that the ovaries of young children, or even of foetuses, show varying degrees of follicular maturation, so that some of the follicular cysts contain considerable amounts of follicular fluid. Corpora lutea are, however, never present. The reproductive cycle does not make its appearance until the still unknown impulse of puberty appears, after which corpora lutea are of course constantly found under normal conditions. This, of course, may be construed as only bearing out what Allen has emphasized, *i. e.*, the follicle is capable of exerting its influence only when it reaches a certain stage of maturity. Otherwise it would be difficult to conceive of its exerting any cyclical influence, inasmuch as there are in every normal ovary during reproductive life a greater or less number of follicles in various stages of maturation.

The general impression which one gains from a consideration of the facts which have been discussed is that a sort of evolutionary gradation of the reproductive cycle has been demonstrated in the results already obtained with the various animals already studied, a gradation not unlike that exhibited by other body functions. In such animals as the opossum and rat, the evidence certainly indicates that the cycle is dominated by the follicle and that the corpus luteum does not become important until after impregnation. In the human, on the other hand, the follicle is of importance in the menstrual cycle, but so is the

corpus luteum, which is well developed in the non-pregnant woman.

Finally, the observations thus far made on monkeys, chiefly by Corner and by Allen, suggest that in these animals an intermediate condition exists, so that in some the follicular type persists, while in others there has been an advance toward the human type. For that matter, it would seem that one and the same animal may at different ages and under different environmental conditions, exhibit differing types of cycle. Even in the human being, if the views I have advanced be correct, there would at times appear to be a persistence of the more primitive follicular form of cycle.

After all, as Meyer says, unless our conception of the teleology of menstruation is all wrong, it would be surprising if the corpus luteum played no part in primary menstruation. If the premenstrual change in the endometrium is really a pre-pregnancy or pre-decidual modification, and if, as is commonly accepted, the corpus luteum plays a definite role in early pregnancy, it would require stronger evidence than now exists to convince one that the corpus luteum of menstruation is not also an important incretory organ. Histological evidence at least would suggest that just as the predecidual endometrium is by an easy transition converted into genuine decidua, so the corpus luteum of menstruation likewise passes directly over to the corpus luteum of pregnancy. It is hard, also, to deny that these two endometrial stages are not both due to the influence of the corresponding phases of the corpus luteum.

The corpus luteum is, in a sense, only a glorified follicle, and it is easy to believe that the function of the follicle is carried as a hang-over into the earlier stages of the corpus luteum. This is, indeed, borne out by the more recent investigations of Allen and others, who find the follicular principle in early but not in the late corpora lutea. But, just because the mature corpus luteum contains none of the follicular element, are we justified in assuming that it has no function whatever in human menstruation? Such a stand is untenable, even though, for the time being, injection experiments with corpus luteum derivatives have proved comparatively unfruitful.

An exception to this statement may be noted in the classical studies of Loeb and the recently published observations of

Papanicalaou. The latter, for example, was able to bring about striking acceleration of ovulation in guinea-pigs by the removal of the corpus luteum, and corresponding retardation of the process by the injection of lipoid-containing corpus luteum extracts. He discounts the importance attached by some to the findings of the follicular hormone in the corpus luteum, inasmuch as the latter apparently produced two hormones. The follicular substance, he believes, is "probably secreted by the undifferentiated theca or granulosa cells, while the specific luteal hormone is probably formed by the fully differentiated luteal cells, the latter increasing in number with the advancing differentiation and development of the corpus luteum."

This explanation, to my mind, is the proper answer to the claims made by Frank and his co-workers as to the unity of action of the follicle, the corpus luteum, and the placenta (the "gestational gland"), based chiefly on the fact that extracts from these organs are synergistic along certain lines. Such an assumption is unwarranted, not only because of the human evidence already set forth, but also because of the demonstration by Papanicalaou of a luteal hormone which possesses a function in many respects quite antagonistic to the follicle substance.

That these two hormones represent a sort of balancing mechanism is indicated furthermore by the recent investigations of Margaret Smith, who was able quite constantly to bring about an interruption of early pregnancy in rats by the injection of follicular extracts. It is during early pregnancy that the corpus luteum shows its most striking growth and is generally conceded to exert an important protecting influence upon the embedding of the fertilized ovum. As Smith says, "It seems quite improbable that the active part of the follicular fluid and the substance produced by the corpus luteum are identical, if the follicular extract injected at this time interferes with the normal development of the fertilized ovum."

As additional evidence against the view that the follicles and the corpus produce only one substance, and that the same, Smith mentions the difference in the effects produced by follicular injections upon ovariectomized and normal rats. In the former, injection soon results in the appearance of cornified epithelial cells in the vaginal smear, and if the injections be kept up daily for two weeks, these cornified cells persist throughout

that time. In the normal rat, however, such an effect cannot be produced, for even though the injections be kept up the normal cycle asserts itself, as reflected in the vaginal smears. The only explanation of this fact would seem to be that the normal ovary contains some element which balances or antagonizes the follicle influence, and which, of course, is lacking in the spayed animal. It seems reasonably certain that it is the corpus luteum which plays this role. Smith mentions an observation which bears out this idea. In four apparently normal animals the follicle injections produced an effect similar to that characteristically found in castrated animals, as above mentioned. Two of these animals were autopsied and their ovaries found to contain large follicular cysts, but no corpora lutea.

May it not be that, in most women at least, the corpus luteum principle is efficacious only in an endometrium already prepared by the follicular substance, as it apparently is under natural conditions? I am speaking, of course, of the human female, because in such animals as the rat, as already stated, the cycle appears to be dominantly a follicular one, the corpus luteum being perhaps more important after the inception of pregnancy. This idea will be alluded to again in the discussion of the therapeutic aspects of the problem.

As might have been expected, one of the earliest results of this newer work on the physiology of the ovary has been an effort to apply it clinically. No criticism can be made of such an ambition, provided that the therapeutic research is based upon sound scientific principles. In spite of the incompleteness of our knowledge of the subject, it is only fair to state that the recent work discussed in this paper offers, perhaps for the first time, something very tangible for clinical experimentation upon the human, and such observations will yield just as valuable evidence along certain lines as will the study of laboratory animals.

It is not my purpose to report statistics as to my results in the comparatively small group of cases which I have thus far had occasion to treat in the light of this newer work, but rather to comment upon certain new viewpoints which these investigations have appeared to inject into the practice of gynecological organo-therapy. My views on the general subject of ovarian therapy,

and they were rather pessimistic, were expressed in a paper which I presented before this Association in 1922.

The chief indications for the use of follicular hormone would appear to be those associated with hypofunction of the ovary. The most important of these are amenorrhea and the subjective symptoms of the menopause. To these may perhaps be added certain types of obesity and certain cases of sterility. Neither of these two latter conditions, however, is associated in a very clear cut way with ovarian deficiency, while the first two named are, and it is to these two alone, *i. e.* amenorrhea and menopausal neurosis, that I have thought it best to limit my own discussion.

The preparation of follicular hormone which I have used is that made by Parke, Davis & Co., to whom I am indebted for a supply of the preparation for experimental use. The substance, as most of you know, is prepared by a technique similar to that recommended by Allen and Doisy, and is standardized on the rat unit basis. At first the ampoules contained only a few rat units, but more recently the strength has been greatly increased, to even 100 units per ampoule, although some deterioration of these stronger preparations is said to occur. No rules can be laid down as to dosage. From a practical standpoint, a daily injection is as much as we can expect the ordinary patient to take, so that, with the earlier weak preparations, the total dosage would seem to have been woefully inadequate.

Amenorrhea of the so-called functional type would appear to constitute the most trustworthy test for the efficacy or inefficacy of the treatment, for here the hoped for results are distinctly objective. At the outset I may say that I have not been able to produce menstruation by the injection of follicular hormone in any of the dozen or so cases which I have thus treated. In most of these, I should say, the extract used was quite weak (varying from 10 to 25 units per ampoule). More recently, however, a much stronger preparation was available, but the results have been the same. Nor have I been able to convince myself of any such noticeable increase in the size of the uterus as Allen and Pratt have reported in a few cases.

These failures were not surprising to me, inasmuch as I have always felt that the follicle hormone, important as it may be, can scarcely be expected to carry the histological cycle of the endometrium to the point where the ensuing involution would

be apt to produce a menstrual hemorrhage. It is conceivable, of course, that very strong dosage over many days might actually cause a hemorrhage of the type described earlier in this paper as of probably follicular causation, *i. e.* the so-called functional uterine bleeding. But I have personally not observed such a result, although a small number of successful results have been reported by others.

More recently I have been attempting to imitate what I believe are the steps occurring in the normal menstrual cycle. As already indicated, it is probable that in the human being the follicle produces the first phase of the cycle, and that the corpus luteum then takes up the process, carrying it up to the time of actual menstrual bleeding. It seems plausible to assume that neither follicle extract nor corpus luteum extract alone can fill the bill—that the follicle produces an effect which is usually insufficient for menstruation, and that the corpus luteum extract exerts its effect only in an endometrium already partially transformed by the follicle influence. A logical plan, therefore, would seem to be to give follicle extracts for a good many days, and then to inject corpus luteum extract, if a good one can be found. At my suggestion, the biological department of Parke, Davis & Co. were good enough to prepare a lipid-bearing corpus luteum extract, this being done by two methods.

These extracts were prepared essentially by the same methods that are known to yield the active lipoids from other parts of the ovary as, for example, from the follicular fluid.

(a) Extract Hog Corpora Lutea.

Ground corpora lutea were allowed to stand over night in two volumes of 75% alcohol. This was filtered, and the residue extracted with hot alcohol (95%). The extracts were combined and distilled in vacuo. The residue was extracted with ether, and after removal of the ether the extract was emulsified in water, in the ratio of 1 cc. emulsion to 4 gm. ground corpora lutea. No physiological standardization was made.

(b) Corpus Luteum Lipoidal Extract.

The method of preparation was the same as the above, except that the ether extract was purified with acetone, and the final emulsion was in a 0.05% solution of sodium bicarbonate. One cubic centimeter of emulsion represented 4 gm. corpora lutea. The estrus-producing power of this extract was approximately 1 rat unit per cc., thus showing that some of the follicular hormone was present. The extract was not tested for corpus luteum activity since no definite method is as yet available for testing this type of activity. For this

reason the extract was put up on the basis of 4 grams of fresh gland to each 1 cc. of final emulsion.

Only six cases have been treated by this method, but it is in this small group that I have observed the most encouraging results. In two of these, menstruation has apparently resulted from a series of injections of follicular extract, followed by a series of injections of the corpus luteum extract. In one case the amenorrhea had been of only four months' duration, so that the importance of the injection in the subsequent menstruation appears less striking than it might otherwise be. This patient was twenty-six years of age, and her amenorrhea was of the so-called hypopituitary type. It was associated with a moderate degree of recently acquired obesity. A menstrual flow lasting three days followed the daily injection for twelve days of the follicle substance, followed by six daily injections of the corpus luteum extract. It is interesting to note that the flow appeared only after the injection of two more follicle substance injections, in a second series following the corpus luteum injections. This case is a recent one, and I merely mention it without any particular stress, as I have not been able to prevail upon the patient to submit to further observations along this line.

The other case, to my mind, is somewhat more impressive. The patient, a trained nurse of 36, had always been irregular in her menstrual history, with periods of amenorrhea lasting as long as six months. Three years ago, however, the periods ceased entirely, and there had been occasional vasomotor flushes, suggesting a premature menopause. There had been no increase in weight. Daily injections of follicle substance alone were given without result, so that treatment was discontinued.

After several months, I prevailed upon the patient to try the experiment of continuing the follicle and corpus luteum substances in the manner above outlined. The treatment presented less practical difficulty than usual, as the injections were given by the resident physician of the hospital with which the patient was associated. Again a dozen follicle substance injections were given, followed by six of corpus luteum extract. No result being obtained, a second series of follicle injections was advised, and here, almost as in the first case, menstruation appeared after one of these had been taken. The patient was encouraged by the fact that menstruation had thus appeared after a lapse of three

years, and was quite willing to keep up the experiments. One week after the flow, which was free and of four days' duration, the injections were again begun, and menstruation again ensued. This was repeated for four months, when the injections were discontinued. Amenorrhea for two months then occurred, following which the injections were resumed, with the production of menstruation once more.

Skeptical though I have been about the value of organotherapy in menstrual disorder, this case appeared to leave little doubt as to the part which it played in this case. I do not know why an exactly similar plan failed in the other four cases in which it was tried. Three were of the so-called hypopituitary type, ovarian deficiency being presumably secondary. The other was a case of functional amenorrhea in a girl of nineteen, with no other discernable endocrin characteristics.

The encouraging result in the two cases above described is mentioned only casually, with no desire to vaunt this plan as a cure of amenorrhea. My own interest in it lies chiefly in the fact that such a method is in accord with what many of us believe is the true explanation of the mechanism of human menstruation, as I have already indicated. At any rate, it would seem worth while to try this method on a wider scale, rather than to draw our conclusions as to the value or lack of value of ovarian organotherapy from the administration of follicle substance alone or corpus luteum extracts alone.

So far as I have been able to judge, such effects as have appeared to follow the employment of the follicular hormone have been of a purely substitutional nature. In other words, no evidence has as yet been obtained to suggest that the substance actually awakens the slumbering ovarian mechanism to renewed activity. For example, in the case above noted, in which the administration of the follicular and corpus luteum substance was followed by the appearance of menstruation, the function failed to persist after withdrawal of the extracts. The same statement may be made with regard to the treatment, by this method, of the menopausal vasomotor symptoms, in so far as the subjective element will permit of conclusions. Whether or not this view is correct must be determined by the study of a far larger number of cases than have as yet been subjected to this form of treatment.

Amenorrhea of the endocrinopathic type is in itself a harm-

less condition, and is compatible with perfect health and well-being otherwise, so that the question which naturally arises with regard to the treatment of many of these cases is "cui bono?" It is hard to persuade women to submit to a long series of daily injections for the treatment of a symptom which, we must admit in all honesty, carries with it no known element of risk. There are two considerations which induce some women to submit to the treatment willingly, or even eagerly. The first of these is the psychic factor, the feeling on the part of some women that absence of the menstrual function defeminizes them and sets them apart from others of their sex. The other is the fact that amenorrhea of this type is most frequently, though not invariably, associated with sterility, so that the real motive for treatment in such cases is the desire for motherhood.

This is of course reason enough to justify efforts along the lines of rational organotherapy, and it is this incentive for treatment which I have most often encountered in the treatment of functional amenorrhea. I shall not here enter into a discussion of the endocrine factors, other than the ovarian, which may be concerned in the production of this type of amenorrhea, such as pituitary, the thyroid, etc. In all of them the amenorrhea is presumably due to a deficiency of the ovarian secretion as the immediate cause, whether this be primary or secondary, so that the ovarian therapy is certainly a rational portion of the treatment.

Where the desire for pregnancy does not exist, the motive for a long continued treatment, especially where this means frequent visits to a doctor's office for the injections, is lacking, and the enthusiasm of such patients is apt to wane long before that of the endocrine factors, other than the ovarian, which may be a tactical disadvantage of the treatment, although it should not deter us in our efforts to carry on these experimental studies on the human female on as large a scale as possible.

As to the effect of the follicle preparation upon the subjective symptoms of the menopause, either natural or artificial, I have been unable to convince myself as yet of any great superiority over the results of the older methods of organotherapy. While the number of cases of this sort which one encounters is naturally larger than those of the functional amenorrhea type, conclusions are hard to reach because of the difficulty of elimin-

ating the psychic factor, and because of the well-known fluctuations in the severity of the vasomotor symptoms exhibited from day to day by the same patient, as I have elsewhere discussed. The uncertainty of this form of therapy would, in fact, suggest that the characteristic vasomotor symptoms may be due to some factor, perhaps of sympathetic nerve mechanism, not attributable to the mere deficiency of the ovarian hormone or hormones.

SUMMARY

Recent investigations on various laboratory animals have tended to stress the importance of the follicle hormone and to minimize the importance of the corpus luteum factor in the oestrous cycle. This change in viewpoint appears to be justified by the available evidence, in so far as the lower animals are concerned.

An analysis of recent investigations upon monkeys, which menstruate much as do women, suggests that in these animals two types of sexual cycle may be observed. One is similar to that seen in the lower animals. It is dominated by the follicle, while the corpus luteum is apparently unimportant. In these cases menstruation may occur without ovulation, but the premenstrual changes in the endometrium are quite unlike those seen at a corresponding phase in the human. The hypertrophic changes are much less marked, and secretory changes are absent.

In the second type, the corpus luteum has the same chronological relation to menstruation as in woman. Ovulation occurs at about the same period, and the premenstrual endometrium is exactly like that in the human, including the secretory features.

In the human the evolution of the function appears to have advanced still further. Both histological and clinical evidence indicates that the prevailing type of menstrual mechanism is that in which the corpus luteum plays an important part, although the follicle is likewise important. Evidence is offered, however, to indicate that even in the human there may at times be observed a persistence of the more primitive follicular type of cycle. These cases constitute the exception and not the rule.

With regard to the therapeutic aspects of the subject, the view is expressed in this paper that the results in the laboratory animals are not applicable to the human patient, chiefly because of the differences in the mechanism of the sexual cycles.

The ovarian follicle hormone, as already indicated, is relatively less, and the corpus luteum, relatively more important in the human than in the lower animals, including monkeys.

Conditions of ovarian hypofunction, such as amenorrhea, furnish the logical indication for ovarian therapy. The employment of the follicular hormone in such cases has not as yet given very striking results, although this form of therapy is in its infancy. The suggestion is made in this paper that the menstrual mechanism be imitated by combining the administration of the follicle and the corpus luteum extracts in proper sequence. This will at least give a very rational basis for treatment, and, if potent extracts are available, will probably give better results than the use of follicle extract or corpus luteum extract alone.

The treatment of amenorrhea by this method is rational, but it presents several serious practical disadvantages. One of these is the difficulty of persuading patients to keep up, usually for a considerable time, a form of treatment necessitating at least daily hypodermic injections for considerable periods. The other is the fact that the condition treated is usually, so far as we know, in itself quite innocuous. The proportion of cases in which such methods of treatment are possible and proper is sufficiently great to yield a valuable human experimental material. While not so readily controllable as laboratory material, the results may prove just as valuable, especially if laboratory results be taken as the point of departure in their interpretation.

It is a pleasure to acknowledge my deep indebtedness to Dr. Carl Hartman, who has so cheerfully nurtured my desire to learn something of the reproductive cycle in the lower animals, and who has made many helpful suggestions in the preparation of this paper. To Dr. George W. Corner and Dr. Edgar Allen I am also under great obligation for their generosity in allowing me to read before publication their forthcoming papers dealing with this general subject.

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CORPUS LUTEUM IN ITS RELATION TO MENSTRUATION AND PREGNANCY*

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CORPUS LUTEUM AND PREGNANCY

The corpus luteum, as a gland of internal secretion, has aroused considerable interest for many years. This conception seemed so plausible, and appeared to be so well supported by experimental evidence, that for a long time it was quite generally accepted as a fact. On this basis many of the phenomena of the sexual cycle and pregnancy were explained. Further, it was responsible for the therapeutic use of various corpus luteum preparations, some of which at first appeared to give quite remarkable results. However, these have come to be almost entirely discredited, and along with this change the conception of the role of the structure as a gland of internal secretion has undergone considerable modification. In the brief space of this paper it is not possible to enumerate all these change, but it is desired to discuss some of the recent studies which show that certain modifications are necessary.

The hypothesis that the corpus luteum is a gland which produces an internal secretion was originated more than a quarter of a century ago. The basis for this assumption was that the histological appearance of the lutein cells, individually and collectively, closely resembled other glands known to produce an internal secretion. Such a hypothesis seemed very plausible, inasmuch as the theory had already been generally accepted that the ovary, as a whole, produces an internal secretion. The endocrine function of the corpus luteum was first proposed by Prenant (1), and soon thereafter appeared the extensive experimental work of Fraenkel (2).

Stimulated by the work of Sobotta (1896) on the origin and evolution of the corpus luteum in mammals, as well as the his-

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tological examination of completely developed corpora lutea, Prenant (1898) concluded that it is an organ by itself—a glandular organ. He suggested two hypotheses: First, it is a gland which puts into the circulation a product, or products which directly modifies the organism in its sexual activities and indirectly affects the entire organism; second, it suppresses ovulation, or renders it abortive, during gestation. Degeneration of the corpus luteum sometime before the end of pregnancy permits preparation for a new ovulation, the approach of which, by reflex action, is the cause of labor.

Fraenkel (2), at about the same time, sought to prove experimentally the hypothesis, suggested by Gustav Born, that the true corpus luteum of pregnancy, on account of its structure and process of development, must be a gland of internal secretion having the function of bringing about implantation and development of the fertilized egg. As a result of his experiments, he suggested further that the corpus luteum is responsible for the increased nutrition of the uterus during the reproductive years; also, for the increase in size and consistency of the uterus during this entire time, as well as the monthly cyclic hyperemia; and further, for implantation of the fertilized ovum and also for menstruation, if fertilization does not occur.

These attractive hypotheses have aroused a great deal of interest ever since they were first proposed. They are at least partly supported by clinical data and clinical observations subsequently collected. There exists quite a uniform conception concerning the anatomical structure of the corpus luteum. This includes the variations in morphology noted at the different stages of the sexual cycle.

At least twenty-five different functions have been attributed to this organ. Many of these already have been discarded, and, therefore, need not be mentioned. It is important to investigate further the relation of the corpus luteum to pregnancy. Many conceptions of this relationship as it pertains to the human are deductions from the results of animal experiments. Such conclusions are not entirely in accord with clinical observations.

Some diversity of opinion exists regarding the length of time the corpus luteum must function to insure implantation and development of the ovum in the uterus of animals. Not all animals are alike in this respect. Fraenkel (2) noted that cauteri-

zation of the corpora lutea in pregnant rabbits prevented implantation of the ovum, if performed during the first seven days after coitus, which act in this animal is necessary for ovulation. If cauterization was delayed until the seventh to the fifteenth day, pregnancy was interrupted.

In the dog and rat, Marshall and Jolly (3) found that removal of the ovaries or cauterization of the corpora lutea shortly after ovulation and fertilization prevented fixation of the ovum in the uterus. They also found that cauterization of all the corpora in these animals was practically equivalent to destroying the ovaries.

Loeb and Hesselburg (4) removed the corpora lutea of guinea pigs three to six days after copulation. They found that abortion had not occurred fourteen to eighteen days after copulation.

Robinson and Asdell (5) studied the relation of corpora lutea to the mammary gland in goats. They stated that removal of corpora lutea in pregnant goats always terminated pregnancy. Their method of extirpation is of interest. The corpus luteum was lifted out, following which the bed from which it was removed was curetted and then cauterized.

Mandl (6) in 1904 performed an interesting experiment. The left ovary of a rabbit was excised three days post-partum and post-coitus. This ovary was transplanted between the abdominal muscles. On October 5th three young rabbits were born alive. November 7th, coitus was repeated. November 9th, the right ovary was removed. November 21st the animal was killed and examined. Eighteen well developed ovular spaces were found in the right uterine horn. In the transplanted left ovary no corpus luteum was found. He concluded that, in the rabbit, implantation and further development of the ovum in the uterus does not require the presence of a corpus luteum.

Unanimity of opinion concerning the function of the corpus luteum in pregnant animals does not yet exist. The necessary requirements for a satisfactory experiment in animals can be fairly well controlled. Some conditions, however, have prevented attaining the ideal, for in most animals the corpora are multiple and comprise a relatively large proportion of the ovaries. If the corpus luteum is not completely removed it tends to regenerate quickly. The methods employed in most experiments, *i. e.*,

cauterization, or excision with cauterization, do not leave a normal ovary. There is some difficulty, therefore, in assuming that the results are entirely due to absence of the corpus.

Clinical data are even more difficult to obtain, for, obviously, similar experiments in the human subject cannot be deliberately planned. But certain necessary operations may contribute either directly or indirectly to the solution of this problem. The influence exerted on the pregnant uterus by removal of one or both ovaries has been of particular value. Oöphorectomy from the end of the second month of pregnancy to its termination has been reported so many times that it is generally accepted that the corpus luteum may be safely spared during this period. The importance of the corpus luteum in the first and second months is more cause for argument.

The importance of protecting the corpus luteum of pregnancy was emphasized by Ochsner (7). Instances were cited by him to show that almost any abdominal operation could be performed without interfering with pregnancy, providing the corpus luteum was not injured. Other operations were followed by abortion, which he considered to be due to the injury or removal of the corpus luteum. Many others support this impression; thus, Mackenzie (8) asserts, but without specific evidence, that removal of the corpus luteum during pregnancy results in abortion.

That abortion *may* occur following interference with the ovaries, no one will deny, but to say that it *will* occur is quite another matter. Ask-Upmark (9) has recently collected records of fifty-one oöphorectomies during the first two months of pregnancy. Seventeen of the women aborted following operation; however, of this number at least nine pregnancies were more or less complicated by other conditions, so that there is some doubt as to whether the operation itself brought about abortion.

Four of the fifty-one cases were of women in the first month of pregnancy. The first subject was operated upon September 6th, 1903. At this time both ovaries were removed. Pregnancy was not suspected during the operation. Just 269 days after the operation a full term child was born. Although the date of the last menstruation was not given, the report is so specific, as regards date of operation and delivery, that one cannot doubt that the corpus luteum and the ovaries were removed during the

first month. The presence of an accessory ovary is not probable, for the pelvic organs were all exposed at operation and, further, there was amenorrhea following delivery.

The second bilateral oöphorectomy was performed before the last menstruation was finished. Pregnancy was not suspected at the time of operation. A full term child was born.

The third bilateral oöphorectomy was accompanied by removal of the tubes on account of inflammation of the adnexæ. The operation occurred shortly after a menstrual period. Pregnancy was not diagnosed until one month after operation. Two hundred and seventy-six days after the operation a full-term child was born.

The fourth oöphorectomy was unilateral, but the corpus luteum was removed with the ovary twenty days after the last menstruation. No corpus luteum was found in the remaining ovary. The pregnancy was apparently progressing normally. The date of delivery was not given.

In addition to these reports from the literature, two somewhat similar cases are reported here:

Case 1: H. R., age 23, had been married six months. No pregnancies had occurred. Menstruation began at 13. It had never been regular, the intervals varying from twenty to thirty days. The flow lasts two or three days, with some pain during the first two.

Examination in July, 1926, showed a normal uterus and adnexæ. There was evidence of hypothyroidism which was thought to have some relation to the irregular menstruation. Thyroid extract was given by mouth. Menstruation occurred August 1st, 1926. Four weeks later a tender mass was noted in the left ovary. On August 31st, 1926, a laparotomy was done. The abdominal viscera were normal. In the pelvis was a normal uterus, slightly enlarged, but consistent with the size expected just before menstruation: The right ovary was normal and did not contain a corpus luteum. The left ovary was about the size of a hen's egg. It was removed. It contained one large cyst and a few smaller atretic follicles. On section the large cyst was seen to be filled with blood and a yellow, stringy material, which appeared to be lutein, containing cells. The lining of the cyst was yellow and velvety. Microscopic section through the large cyst showed the lining to be composed of large, light pink staining, luteal cells. There were also atretic follicles and corpora fibrosa.*

Subsequent to operation menstruation did not recur for, as was found later, pregnancy already existed at the time of operation. On May 7th, 1927, just 279 days after the last menstruation, a full-term

* Microphotographs were demonstrated by lantern slides.

child was born. Labor was normal and the patient was able to nurse the child normally.

The corpus luteum was larger than average, due to the increased amount of blood which it contained. It is obvious, however, that this was the only recent corpus luteum and that pregnancy continued without the proper corpus luteum after the thirtieth day succeeding the last menstruation.

Case 2 (mentioned in another paper, 10): Mrs. M. Mc., age 23, had been married five years. Her chief complaint was sterility. Three previous pregnancies all terminated at the seventh month. She was very desirous of having a normal, full-term child. General physical examination revealed nothing abnormal except in the pelvis. There was a deep bilateral laceration of the cervix with a retroversion of the uterus and slight descensus. The last menstruation occurred twenty days before operation. At the time of operation the cervix was repaired, the uterus suspended, and the appendix removed. Both ovaries were carefully examined and in the left one a large corpus luteum was found and removed. The raw area was covered over with sutures. This was the only corpus to be found in either ovary. A careful examination was made to determine this, for it is known that more than one corpus may be present at the same time.

Inasmuch as menstruation occurred just twenty days previous to operation, it was not considered that pregnancy could exist, for the appearance of the uterus gave no such indication. Therefore, it seemed perfectly safe to remove this corpus luteum for study. The particular interest at this time was to determine whether or not there was any hormone present in the corpora. This specimen was sent to Dr. Edgar Allen, who made sections and also extracted it to determine the amount of hormone present. It was found to contain more than 1.5 rat units. Microscopic examination showed a typical corpus luteum fully developed.*

Menstruation did not occur within the next two or three days, as was anticipated when the corpus luteum was removed. Later it became obvious that the patient was pregnant. The uterus enlarged consistently with the duration of pregnancy dating from the menstruation just preceding operation. Two hundred and seventy-two days after the last menstruation, a normal eight-pound baby was born. The course of pregnancy and delivery was normal in every way.

With reference to the last case, the objection may be raised that the corpus luteum was not all removed or that there was more than one true corpus luteum present, although only one was removed. In answer to these, it may be said that the corpus shelled out easily, leaving a clean surface. Sections made for microscopical examination showed that removal of the lutein cells

*Microphotograph of corpus luteum removed at operation was demonstrated on lantern slide.

was complete and that the capsule from the theca was also present. Whether or not there was another corpus luteum left in the ovaries is not so easy to prove. It is certain, however, that only a very small one could have been overlooked, and even that is very improbable, for careful search was made at the time of the operation because of interest in the relation of the corpus luteum to menstruation. The ovaries were both average size and were easy to examine. By comparison with many other similar ovaries it seems certain that no other corpus was present, except those associated with previous menstruation, and there is no reason to believe that such corpora are active.

Although corpora lutea are known to have been removed during the first month of pregnancy, it is still uncertain what relation this bears to the actual implantation of the ovum, for it is not known how long it takes the human ovum to reach the uterus. One might infer from observation in animals that this period of transit is about three days. Such an inference, however, is only speculative.

The relation of ovulation to menstruation is just as fundamental to this problem as is the time of transit. Not all observers agree but there is much evidence to show that ovulation occurs about midway between two menstruations. Shroeder states that ovulation takes place about fourteen to sixteen days after the onset of menstruation. Shaw (11) confirms this, but gives a somewhat wider variation. Our own findings at operation have shown recently ruptured Graafian follicles from the twelfth to the eighteenth days, with the majority about the fourteenth or fifteenth day. While the most accurate method is actually to see a recently ruptured follicle, further evidence can be obtained by finding corpora lutea in a similar stage of development at a given interval after menstruation. Although Corner has recently stated that menstruation may occur in monkeys without ovulation, this is not the rule in women.

Evidence of the function of the corpus luteum in pregnancy is furnished in an indirect manner by the procedure of De Lee (12), who transplanted a corpus luteum removed in one instance forty-two days and another, fifty-six days after the last menstruation. Abortion occurred shortly after operation in both of these cases. It is not certain that those grafts lived, but it has

been repeatedly shown that the corpus luteum may be successfully transplanted.

That pregnancy could occur without the presence of a corpus luteum in either ovary was supported by Abbott (13), who examined both ovaries of a pregnant woman without finding a corpus luteum in either.

CONCLUSIONS

With reference to the relation of the corpus luteum to pregnancy, it would seem to appear, during the latter months of pregnancy, that the successful development of the fetus in the human uterus does not require the presence of the corpus luteum, and there is considerable doubt as to its importance even for successful implantation of the ovum. The following reasons support this:

1. Many instances are reported in which the ovaries were removed during the latter months of pregnancy without any apparent disturbance.

2. Even in the first month of pregnancy the corpus luteum in at least five instances has been removed with the ovary without abortion occurring.

3. During the very time when implantation of the ovum is generally considered to occur, it has been removed without interfering with a successful implantation.

4. Once in the rabbit (Mandl, 6) and once in the human (Abbott, 13) pregnancy has occurred without evidence of a corpus luteum in the ovary. The administration of preparations of corpus luteum in toxemias of pregnancy must be based on the assumption that a deficiency of corpus luteum exists. There seems to be no concrete evidence to support this assumption, for early removal of the gland has not been followed by toxemia.

5. The danger of abortion following an operation involving the corpus luteum has been exaggerated, for it is generally known that abortion may occur following any operation.

CORPUS LUTEUM IN RELATION TO MENSTRUATION

Irregularity in the interval, amount, or duration of menstruation is a problem with which the clinician is frequently confronted. Solution of such a problem requires a clear understanding of normal menstruation. As yet, however, all theories advanced in an effort to explain the cause for onset of menstruation are open to various criticisms.

It is generally accepted that the ovaries are responsible for periodic changes. This conception is supported by results of radiotherapy, for ovaries, which have been radiated, show complete, or partial, destruction of some of the epithelial elements, the changes varying in accordance with the dosage. If the larger follicles and corpora lutea are destroyed, with only atretic follicles remaining, the uterus maintains its development, but menstruation is delayed until mature follicles and corpora lutea are again formed.

Should the atretic follicles be excluded, the developing follicles and corpora lutea, singly or both together, remain to be considered as controlling factors. It is of interest, in this connection, to note that from follicles, corpus luteum, and placenta an identical hormone may be isolated, which, upon being injected into spayed animals, substitutes for all phases of oestrus. This hormone, when injected into women from whom both ovaries have been removed, has not yet produced a normal menstruation; it has, however, caused softening of the uterus and some enlargement, and in certain instances reproduced some of the subjective symptoms of menstruation.*

Primary amenorrhea, *i. e.*, failure of menstruation to appear up to the age of twenty or more, has not been relieved by injection of this hormone; however, in these individuals perceptible changes in the uterus have been noted. It is of interest to note that at operation corpora lutea were found in the ovaries of two of the subjects with primary amenorrhea. In one of these there was tuberculosis of the endometrium, but not all of the endometrium had been destroyed by the disease. In the other, the uterus appeared to be normal, and therefore was not removed; hence the condition of the endometrium is not known. Observation in still another individual in whom there was complete amenorrhea showed an apparently normal uterus with a corpus luteum in the ovary. The cause of amenorrhea in these three women has not been explained.

In a third group of patients, who had scanty and irregular menstruation, the results of injection of hormone have been more striking but have not been constant. Some of this group had symptoms of hypothyroidism and the administration of

* The hormone used for experiments was furnished by the experimental laboratories of Parke, Davis & Co. and of E. R. Squibb & Son.

thyroid extract alone has been more effective than use of the hormone. In other instances the hormone has produced better results than thyroid extract. The best results have been obtained by a combination of the two therapeutic agents when both hypothyroidism and hypoövarianism were present.

In earlier studies, it was considered that the small dosage might account for the meager results. This has not been substantiated by employment of larger amounts of the hormone, for with injection of the larger dose more of the hormone can be recovered from the urine, but neither is the menstrual flow increased, nor the irregularity of the interval improved. During the normal menstrual cycle, varying amounts of the hormone may be recovered from the urine. Results of quantitative tests of urine are not yet available. In addition to finding the hormone in urine, it is found in other body fluids. Frank (14) has shown that this hormone is present in the blood of normal women.

Since the hormone can be obtained from both the mature follicles and the corpus luteum, results obtained from study of the hormone do not help differentiate the importance of the two structures. In fact, it would lead to the conclusion that they have something in common. Perhaps the function started by the follicle is continued in the corpus. This might be expected since the lutein cells have their origin in the membrana granulosa.

Results obtained by extirpation of the corpus luteum in various phases of the menstrual cycle give some evidence as to the function of the corpus luteum. This procedure has been carried out many times by various observers. There is, however, no agreement as to the results obtained. This is difficult to explain, since the procedure is simple and the results should not be hard to interpret.

Fraenkel (2) cauterized follicles or corpora lutea in nine cases. He asserted that by removing the corpus luteum, or preventing its development, the next menstruation is delayed.

Corpora lutea and active follicles were removed in sixty-five cases by Ostreil (15). His method was excision of a wedge shaped piece of ovary containing the corpus and, if necessary, incision of the other ovary to ascertain the possible presence of a corpus luteum. In most instances when the excision occurred

during the first half of the menstrual interval, he found that the next menstruation occurred quite near the expected time, the delay being only one or two days. Excision from the 4th to the 21st day caused a delay of 14 to 28 days. Excision after the 21st day in most instances induced bleeding within two days.

Seitz and Wintz (16) found that in 11 of 12 cases removal of corpus luteum during the second half of the menstrual interval was followed by flowing on the second day, and that in 13 out of 15 cases the removal of large follicles during the first half of the interval induced menstruation within three and a half weeks.

In forty cases, Halban and Koehler (17) removed corpora lutea by incision and blunt dissection. In 92.5 percent of these, flow appeared from 2 to 4 days following operation and had a duration of 3 to 8 days. The duration and intensity corresponded to the normal menstrual type of the patient. When the next menstruation occurred it was usually at the regular interval after the induced menstruation and not the flow preceding operation.

In two of these cases in which the ovaries were removed the same phenomenon was noted as regards onset of flow, its occurrence being within two days and naturally followed by amenorrhea.

In thirty cases we have removed the corpus luteum from the ovary by method of incision and blunt dissection. Careful inspection has been made to insure complete removal. In most instances this is not difficult for the corpus luteum shells out of its bed, leaving a clean surface. In all but two of these cases removal of the corpus luteum was followed by an induced flow within forty-eight hours. In most instances the amount and duration of this flow closely corresponded to the normal average of the individual. It has not been possible in all instances to determine the onset of the succeeding menstruation, but, whenever this information was obtained, the interval between the induced flow and the next menstruation has been the average for that individual. In 11 instances the corpus luteum with the entire ovary in which it was contained has been removed. The results obtained were similar to the results following removal of the corpus luteum alone. In this series of forty-one cases, the results have been the same regardless of whether the corpus

luteum was removed during the first half or the second half of the menstrual period.

The influence of bilateral oöphorectomy has been observed in three instances. Two of these removals occurred during the first half of the intermenstrual interval. Induced flow appeared on the second day and simulated, both in amount and duration, a normal menstruation. The third bilateral oöphorectomy was done on the sixth day after the onset of menstruation. In this instance there was no induced flow. Our results in removal of the corpus luteum tend to confirm the findings of Halban and Koehler (17). Regardless of whether the corpus luteum was removed alone, or with the ovary in which it was contained, the flow, with two exceptions, was induced within two days. In one instance the appearance of the flow was delayed until the sixth day and in one of the bilateral oöphorectomies there was no flow at all following the operation.

Similar findings are reported by Ochsner (7), who in two instances removed the only remaining ovary. In one of these cases the previous menstruation had occurred ten days before operation and the induced flow began twelve hours after operation. In the other case the previous menstruation had occurred fifteen days before operation and the induced flow appeared about thirty hours after operation.

Summary and Discussion

Whether or not the flow induced by removal of a corpus luteum, represents a real menstruation is a question which can be satisfactorily answered only after making a histological examination of the tissues to determine the existing condition of the endometrium. In no case has it seemed indicated or justifiable to perform curettage to obtain material for such an examination. However, the question may be partly answered by two observations: first, the amount and duration of the induced flow is usually similar to the average menstruation for that individual; second, the succeeding menstruation usually occurs at the expected interval, reckoning from the time of the induced flow.

Discrepancy in the reported results following removal of corpora lutea may be explained by the difference in the method by which they were removed. Where cauterization is employed

the specimen is destroyed and no histological examination can be made. When this method is used diagnosis of the state of the corpus luteum can only be made from the gross appearance before it is removed from the ovary. A further objection to this method is that it is difficult to be certain when the whole corpus luteum is destroyed and whether the remainder of the ovary is not injured.

Excision of the corpus luteum is to be preferred; for this method permits inspection of the specimen at the time of removal as well as after it has been removed, and little or no damage is done to the remainder of the ovary.

The choice of method of removal is of considerable importance, for it is not always possible to determine the state of development of the corpus luteum without histological examination.

The possibility of substituting for the function of corpus luteum after its removal has been studied by Halban and Koehler (17). They transplanted the corpus luteum immediately after its removal in nine cases. The results of such a small series are not conclusive, but are suggestive that such substitution is possible. There is a further difficulty with their experiment, inherent in the fact that they produce no proof that the transplant survived.

Since a definite hormone may be extracted from the corpus luteum, it occurred to us that injection of this hormone immediately after excision of the corpus luteum might change the effect of removal. Injections were made as often as every eight hours, beginning within two hours after operation. As much as three hundred rat units were used, but the results were negative for the induced flow appeared at the usual time. It would seem from these results that there is probably more than one hormone concerned with menstruation.

It may be concluded that the corpus luteum is an important factor in controlling the menstrual cycle, but its exact role cannot yet be assigned. Whenever a corpus luteum is removed, either by itself or with the ovary in which it is contained, the next menstrual interval is disturbed. While observations reported in the literature do not entirely agree, the preponderance of evidence indicates that this disturbance is usually in the

nature of an earlier period, which establishes a new cycle of menstruation.

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CLINICAL MANIFESTATIONS OF WATER INTOXICATION IN A CASE OF SEVERE DIABETES INSIPIDUS,
WITH SOME NOTES ON THE DISTURBANCES OF
BLOOD COMPOSITION AND VASOMOTOR
MECHANISM*

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In 1922, Weir, Larson and Rowntree described certain symptoms of water intoxication in a case of diabetes insipidus; the symptoms occurred after the administration of pituitary extract, the patient in the meantime taking water on request in the amounts to which he had become accustomed. In eight hours 5250 cc. of fluids was consumed, and 800 cc. of urine was passed; the nausea, vertigo, severe headache, and slight edema of the face and ankles resulted. Repetition of the experiment on the same and on another patient produced similar results. In 1923, Weir reported further studies on this peculiar form of intoxication and demonstrated a coincident increase in the relative volume of blood plasma. Rowntree conducted extensive experiments on the effect of the administration of excessive amounts of water to the experimental animal. He has produced ataxia, vomiting, and convulsions by this means, and Greene and Rowntree have demonstrated the fact that actual dilution of the blood may occur.

The relation of heat regulation to water metabolism has been studied by various investigators and its essentials have been reviewed by Barbour. Greene and Rowntree have recently demonstrated a decrease in body temperature in water intoxication and have shown that this result is largely independent of the temperature of the water used. Depression of body temperature may be produced by the ingestion of excessive amounts of water at body temperature and even by water up to 42°C.

* Read before the Association for the Study of Internal Secretions, Washington, D. C., May 17, 1927.

Rowntree has also mentioned the "heat liability" which patients with diabetes insipidus incur by taking large amounts of ice-water, and has noted the clinical symptoms such as shivering, weakness and tremor caused by this practice. He also noted that these symptoms may be relieved by the substitution of warm for cold water.

Since the physiologic factors involved in water metabolism and heat regulation are individually of such great importance, and particularly since their interrelation in the experimental animal has been demonstrated by the recent work of Greene and Rowntree, we have been interested in securing clinical data bearing on these points. An opportunity recently presented itself in the form of a patient suffering from severe diabetes insipidus secondary to epidemic encephalitis. The exceptionally severe character of his disorder, the presence of uncontrollable thirst, and the relative ineffectiveness of pituitrin in the control of the polyuria, made him a favorable if somewhat uncoöperative subject. He presented symptoms and signs of water intoxication which furnished a fairly complete clinical counterpart of the syndrome of water intoxication observed in experimental animals; there was also evidence of a compensatory effort at heat regulation in consequence of the "heat liability" incurred by the ingestion of great quantities of ice-water. The case is reported because of its unusual interest from the standpoint of physiology and clinical medicine.

HISTORY OF THE CASE

A man, aged twenty-seven years, a railroad station agent, had been well prior to the onset of his present illness except for severe influenza in 1918. In March, 1923, weakness, diplopia, and easy fatigability were noted, and the patient, at the suggestion of his physician, drank rather large amounts of water. In November of that year he experienced a desire for water which he says was "not a real thirst"; the excessive intake of water soon amounted to six gallons (24 liters) a day, and a proportionate amount of urine was voided. During the following three years he worked at times but was weak, listless and, according to his family, increasingly inefficient. This gradual deterioration was substantiated by his gradual decline in the estimation of his employers; he had been removed from several positions and transferred in each instance to one carrying less responsi-

bility. His family had also noted a change in his personality, his disposition becoming morose and gloomy. The polydipsia and polyuria continued as before and at times were very severe; the patient mentioned that he had taken 15 gallons (60 liters) of water in a single day. In spite of an excessive appetite he had lost a good deal of weight. In June, 1926, following a period when weakness and lassitude had been particularly troublesome, he recalled the advice of his physician in regard to drinking water, and reasoned that if cold water was good for him, more and colder water might cure him. He therefore filled two buckets with cracked ice and consumed ice-water as rapidly as possible, drinking from one bucket as the other cooled. He recalls vomiting at this time, and finally had a convulsion while the bucket from which he was drinking was still in his hands. According to the patient's wife, the convulsion was epileptiform in type and was followed by deep coma. Recovery, however, was prompt, and the patient tried his ice-water treatment again with the same result, vomiting and convulsions. He had experienced six convulsions between June, 1926, and the following January, in each instance falling over with the bucket in his hands. The diagnosis of epilepsy seemed justified until the relation of drinking bouts to these convulsions was established.

The outstanding features on physical examination were those related to the encephalitic residue; the parkinsonian facies, slow clumsy muscular movements and coarse tremor were striking. The extremities were cold, dry and markedly cyanotic, and the patient was shivering constantly. The pupillary reactions and visual fields were normal and the ophthalmoscopic examination negative; the teeth were poorly kept, and the tonsils infected. There was no peripheral arteriosclerosis, the heart was normal, and the systolic blood pressure was 122, the diastolic 78. Respirations were often of a "grunting" type, and the patient coughed and cleared his throat repeatedly; the lungs, however, were clear. Abdominal examination revealed nothing of importance; the kidneys were not palpable. The deep reflexes were normally active and equal; there was no Babinski sign. The output of urine was 24,000 cc. in twenty-four hours; the urine was otherwise normal except for the specific gravity 1.001. The hemoglobin was 80 (Dare); erythrocytes numbered

5,000,000, and leukocytes 9,000; the differential count was normal. Blood and spinal-fluid Wassermann tests were negative. Roentgenograms of the skull and long bones did not show abnormalities. The blood urea was 14 mg., the total blood fats 284 mg., and the serum proteins 8.35 gm. for each 100 cc. of blood. Four readings of the metabolic rate, none of them entirely satisfactory because of involuntary muscular movements, averaged $+30$; this observation was of interest since in our experience practically all cases of secondary diabetes insipidus are associated with lowered basal metabolic rate.

Epidemic encephalitis, with the parkinsonian and respiratory syndromes, and secondary diabetes insipidus was diagnosed and the patient transferred to hospital for detailed study January 27, 1927.

For convenience and clarity in presentation, the course in the hospital will be considered from three standpoints: (1) the effect of pituitrin on polydipsia and polyuria; (2) the evidence pointing to water intoxication as a complicating factor, and (3) the "heat debt" and the mechanism of heat regulation.

EFFECT OF PITUITRIN

The effect of pituitary extract and the mechanism by which it controls the polydipsia and polyuria of diabetes insipidus have been under discussion since von den Velden and Farini and Ceccarino first described its antidiuretic effect. The mechanism by which this effect is exerted is still unknown, but the extract is active in controlling the symptoms in practically every case. In a large series of cases at the Mayo Clinic, only one other case has been observed in which the cardinal symptoms could not be effectually controlled by its use; this case also was secondary to epidemic encephalitis. In the present case, pituitrin controlled the polyuria only slightly; the polydipsia was apparently unaffected. The patient's thirst was apparently primary, and his case corresponded to the type discussed by Ebstein and others in which the primary occurrence of thirst was a feature. It seemed to be a sort of "compulsion" thirst, similar in nature to the compulsion hyperpnea observed in the respiratory syndromes associated with encephalitis. The extent to which the water balance was affected by this peculiar type of thirst, and the lack of effectiveness of pituitrin in its control is illustrated in Figure 1. The normal response of a

moderately severe case of diabetes insipidus is included for comparison.

WATER INTOXICATION

The untoward effects of excessive ingestion of water were first described by Miller and Williams. They noted vertigo, headache, and vomiting in cases of chronic nephritis in which large quantities of water had been ingested. The observations

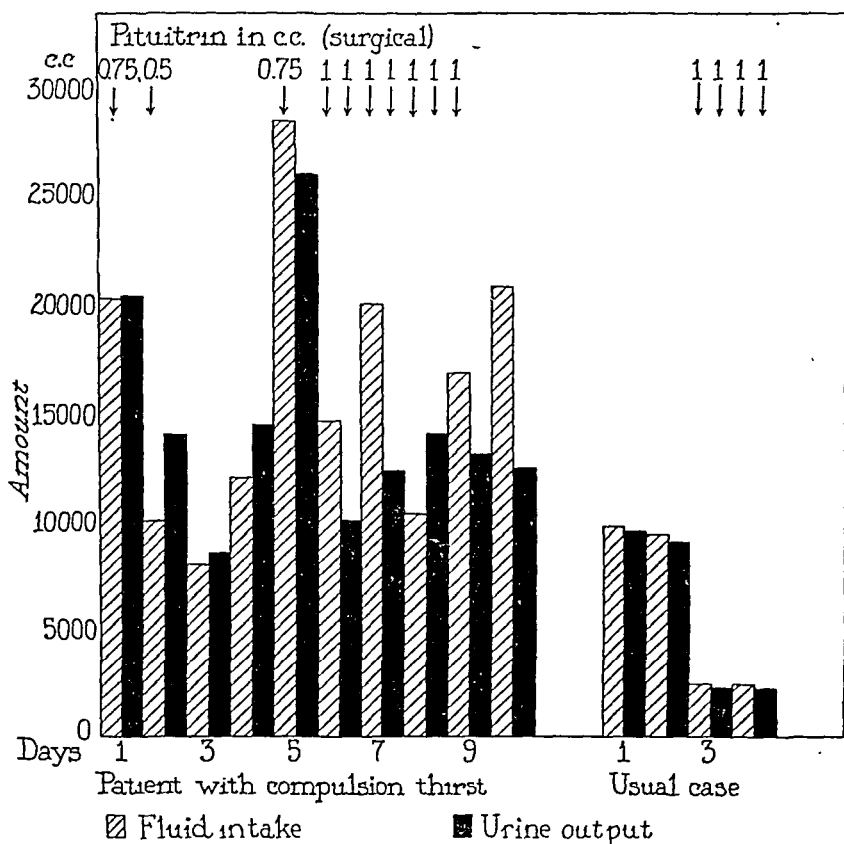


Figure 1. Pituitrin in diabetes insipidus.

of Weir, Larson and Rowntree have already been mentioned; they were the first to describe a condition of water intoxication in connection with diabetes insipidus, and also were the first to produce this condition experimentally. In their experimental work, pituitrin was given prior to the administration of water in order to decrease the output of urine. They postulated a disturbance of the salt and water equilibrium of the body as the

fundamental cause of the convulsions observed. Rowntree subsequently produced the condition in the experimental animal without the aid of pituitrin. In his animals, restlessness, asthenia, diarrhea, salivation, vomiting, tremor, ataxia, tonic and clonic convulsions, stupor, and coma occurred, and continuation of the excessive intake of fluid usually resulted in death. Greene and Rowntree have also demonstrated a dilution of the blood in these animals, as shown by a decrease in hemoglobin, serum protein, viscosity, electrical conductivity and molecular concentration. There was an increase in both the body weight and in the plasma volume. The content of chlorides and sodium and potassium in the serum was diminished out of proportion to the degree of dilution of the blood. The last mentioned observations have been confirmed by the work of Underhill and Salick.

The history of the convulsions in our case suggested that water intoxication and not epilepsy may have been responsible. While the patient was in the hospital, further evidence on this point was obtained. During the first three days of his stay, the intake of water fell greatly. This was due chiefly to our request that he take only what he needed to control his thirst. On the fourth day he disregarded advice and began to take water in greater quantities; on the fifth day the water exchange reached a level of 26,000 cc. On the sixth day 1 cc. of surgical pituitrin was given at 8 A.M. and at 5 P.M.; the intake exceeded the output by 4600 cc., and toward evening the patient was confused, tremulous, and very uncomfortable. He passed a fairly good night, but on the following day his desire for water was uncontrollable. One cubic centimeter of pituitrin (surgical) was given at 8 A.M. without effect on the thirst, and between this time and 5 P.M. he consumed about 16 liters of ice-water; at 5 P.M. he said he felt exactly as he did before the previous convulsions. He was restless, confused, and agitated, the face was flushed, and muscular movements poorly coordinated. There was slight ataxia, but no visible edema. He was put to bed at once and given 1.5 grains of phenobarbital; the intake of water was rigidly restricted. The following morning he felt much better and was able to control his thirst voluntarily on this day. There was a negative fluid balance of 4200 cc. in spite of two doses of surgical pituitrin of 1 cc. each. On the last two days of his stay in hospital, pituitrin was not given; the fluid balance

again became positive and the former symptoms of restlessness and confusion were apparent.*

The changes in the blood, the fluid balance, and the weight curve are summarized in Table 1. The complete picture of water intoxication in man has never been described, so far as we are aware, and we do not consider this case a perfect example. However, much clinical and laboratory evidence pointing to true water intoxication was obtained. The history of convulsions following the ingestion of great quantities of water is unique in our experience; while the encephalitis may have been partially responsible, water intoxication seems the more reasonable explanation. During a period when the patient was under our observation, he consumed 17,200 cc. of fluid in excess of the output of urine, gaining 9 pounds (7 per cent of the body weight), in four days; at the conclusion of this period toxic symptoms similar to those already described were noted. At this time there were also evidences of blood dilution, as shown by the reduction in the serum protein (13 per cent), the reduction in blood chlorides (20 per cent), and the decrease in blood sodium (27 per cent). The relative plasma volume, as shown by the hematocrit, was increased 8 per cent, and the whole blood volume, as measured by the method of Keith, Rowntree, and Geraghty, showed an increase of 4 per cent. (The latter reading is within the limits of error for this method.)

It has been shown by Weir that patients with diabetes insipidus present slight and somewhat inconstant evidences of blood dilution after the administration of pituitrin. We have had the opportunity to study one other case with reference particularly to the serum sodium and chloride. The data obtained from this case (Case 2), from Weir's cases (Cases 3 and 4), and from the case presented in this paper are compared in Table 2. It will be noted that in no other case did so great a decrease occur in the concentration of both electrolytes and serum protein.

The last reading obtained in our case (Table 1), deserves a word of explanation. The blood samples were taken during a period when the intake was about 5000 cc. in excess of the output, although no very definite symptoms of toxicity were noted.

*A letter received recently stated that the patient has had no further convulsions and he has voluntarily restricted the intake of water.

TABLE I
CHANGES IN THE BLOOD DURING DIFFERENT PHASES OF WATER INTOXICATION (CASE 1)

PHASES OF WATER INTOXICATION (CASE 1)													
Date, 1927	Weight, pounds		Fluid		Pituitrin, surgical c.c.	Chlorine, mg. for each 100 c.c.	Sodium, mg. for each 100 c.c.	Osmometer reading, mm. of water	Serum protein, gm. for each 100 c.c.	Plasma volume, c.c. for each kilogram	Whole blood, c.c. for each kilogram	Acid hematin hemo- globin, gm. per cent	Remarks
	Intake, c.c.	Output, c.c.											
1/27	132	21000	21050	0.75									
1/28	132½	10000	14000	0.50	590								
1/29	132	8000	8500	None	670	395	51.2	8.35	60		107	16.8	
1/30	129	12000	14400	None									
1/31	129½	28400	26000	0.75		385	43.0	8.16					Relatively normal.
2/1	131½	14600	10000	2.00									
2/2	138¾	20000	12200	2.00	530	288	40.2	7.20	54		111		Phase of acute water intoxication.
2/3	141½	10200	14000	2.00									
2/4	121	16800	13000	1.00									
2/5		5200*	3100*	None	530	283	51.3	7.95	56		103	17.1	Mild symptoms of water intoxication.

*Six hours only.

*Six hours only.

TABLE II
COMPARISON OF CHANGES IN THE BLOOD IN VARIOUS CASES OF DIABETES INSIPIDUS

Author	Fluid		Pituitrin medication, c.c.	Hematocrit plasma, per cent	Serum protein, gm. for each 100 c.c.	Sodium chloride, mg. for each 100 c.c.	Sodium	Chloride	Remarks
	Intake, c.c.	Output, c.c.							
Weir, Case 4	6705	6107	None	62		600			
	2865	1942	1, obstetric	57		573			
			None	58	6.85	555			
			1, obstetric	71	6.25	551			
Weir, Case 3	5180	4525	None	67	7.31	648			
	3193	915	2, surgical	69	6.75	640			
	2380	1200	1, surgical	72	6.63	623			
	4732	4443	None	71	6.85	633			
	9750	9500	None						
Rowntree, Case 2.	9250	9000	None		7.50		409	740	
	2500	2250	2, surgical						
	2500	2250	2, surgical		8.00		364	630	
	8000	8500	None	56	8.35		395	670	Relatively normal.
Snell and Rowntree, Case 1.	20000	12200	2, surgical	59	7.20		288	530	Phase of water intoxication.
	5200*	3100*	None	55	8.00		283	530	Mild symptoms of water intoxication.

*Six hours only.

The values for electrolytes were slightly less than those obtained during the phase of water intoxication, whereas concentration of the serum protein and hemoglobin and the osmometer readings were about normal for this patient. A high concentration of serum protein and high osmometer readings characterized this case in all phases. It is probable that the electrolytes are the first elements of the blood to be disturbed by excessive intake of fluid, the proteins being influenced in a relatively slower manner and to less extent.

It has been shown in studies on water intoxication in the experimental animal that there is a decrease in serum protein of about 15 per cent and a reduction in electrolytes of about 25 per cent. This corresponds almost quantitatively to the changes observed in our patient; during the period of water in-

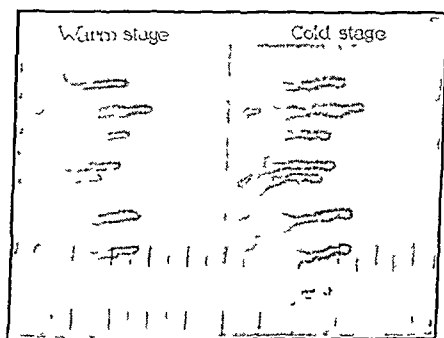


Figure 2. Nail-fold capillaries in diabetes insipidus.

toxication he also showed a greater fall in serum sodium and serum chloride than in any case of which we have a record. In conclusion, the enormous water balance, increase in weight and history of previous convulsions furnish additional support to the view that this was a case of true water intoxication.

DISTURBANCES OF HEAT REGULATION

The cold, cyanotic extremities and the constant shivering noted in this case were recognized as being due to a disturbance in the heat regulating mechanism. On his first day in the hospital a four-hour specimen of urine measured 5050 cc., a second four-hour specimen obtained after the administration of 0.75 cc. of surgical pituitrin amounted to 2000 cc. During this second period the hands became warm and pink, the shivering stopped abruptly, and the oral temperature rose to 99°F. He also per-

spired freely at this time. This remarkable occurrence prompted a further study of the heat debt which was incurred by the ingestion of large quantities of ice-water. The actual caloric debt in this case was calculated as varying from 315 to 1070 calories, depending on the amount and temperature of fluid taken, the average being about 660 calories. The food requirement was calculated as follows:

Basal requirement (1554 calories) + 30 per cent (elevation of basal metabolic rate) (466 calories)	=2020 calories
Specific dynamic action of food (10 per cent)	200 calories
Muscular exertion (20 per cent).....	400 calories
Average requirement for raising temperature of water	660 calories
Total	<u>3280 calories</u>

As a matter of fact the patient exhibited definite bulimia, reminiscent of Trousseau's celebrated case, and took food equivalent to about 4000 calories daily. The increased food requirement caused by the patient's heat debt probably produced a demand for food in excess of the amount actually required to raise the temperature of the ingested water. Such overcompensation might be expected and, if it occurs, would fully account for the excessive intake of food. Other factors which might be called into play to compensate for the heat debt in such cases are muscular movement and peripheral vasoconstriction. The former, as evidenced by shivering, was noted in this case, also about in proportion to the amount and temperature of water consumed. The vasomotor changes were studied in greater detail.

As has been previously stated, the reduction in water exchange effected by pituitrin caused a marked rise in the temperature of the body generally and a definite change in the color of the hands, from dusky and cyanotic to that of definite rubor. The nail-fold capillaries were studied in both phases on subsequent days. In the cold stage, the capillaries were dilated, with some cyanosis; the flow was slow and intermittent and a definite loss of tone was observed, the whole picture indicating arteriolar constriction. In the warm stage the capillaries were contracted, although loss of tone was still obvious. The flow was more rapid and homogeneous; cyanosis was not present in the capillary blood. These changes are represented in Figure 2.

The skin temperature was measured by the thermocouple. When the patient was taking ice-water freely, the temperature of the upper extremities was but little above that of the surrounding air. After the administration of pituitrin, during comparatively brief periods when thirst and polyuria were partially controlled, the temperature of the extremities rose from 5° to 15° Centigrade (Figs. 3 and 4). It must be remembered that these temperature readings are recorded during the period of one hour only, and consequently cannot be correlated accurately with the twenty-four hour output of urine. The hands were often warm and of good color after the morning dose of pituitrin, and cold and cyanotic by night. In general, the cold

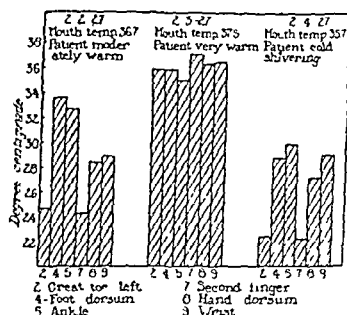


Figure 3. Surface temperatures in diabetes insipidus.

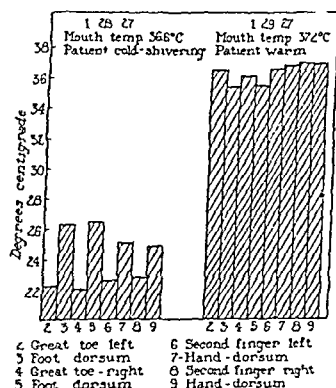


Figure 4. Surface temperatures in diabetes insipidus.

stage was less pronounced during periods of negative water balance, although it could be precipitated at almost any time by the patient, who was in the habit of taking three or four quarts of ice-water in a few minutes.

In order to obtain further evidence in regard to the elimination of heat in the extremities, studies were made with the Stewart-Kegerreis calorimeter. The heat production of the lower extremities is represented graphically in Figure 5; the lower reading was obtained January 31, the intake of fluid being 28,400 cc. and output 26,000 cc. on that day. The heat production a minute for each square inch of surface was 0.58 calorie, about comparable to that of a patient with advanced thrombo-angiitis obliterans or marked Raynaud's disease. The higher reading, which represents a normal heat elimination of 1.03 calories a

minute for each square inch of surface, was obtained February 30, the intake being 10,200 cc., and the output of fluid 14,000 cc. on that day. Here, as with the skin temperature, the negative water balance and relatively low intake of water after the administration of pituitrin seemed to accelerate the elimination of surface heat because of increased peripheral blood flow.

Calorimetric studies on the upper extremities gave a curious result, which is represented graphically in Figure 6. A normal curve of heat production in the hand is included for comparison. It will be seen that the hands tended to assume the temperature of the water in which they were placed; if warm when placed in the calorimeter, they produced a momentary rise of temperature, followed, after a short interval, by a fall. In this respect the upper extremities behaved as would those of a poikilothermic

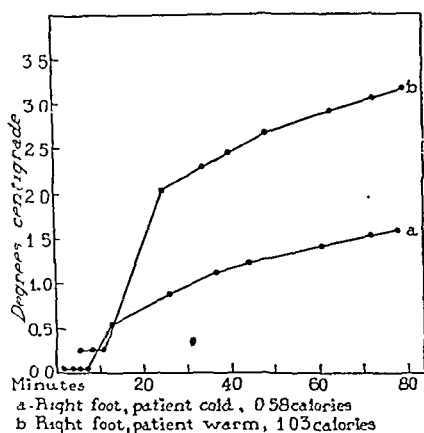


Figure 5. Calorimetric studies of the lower extremities in diabetes insipidus.

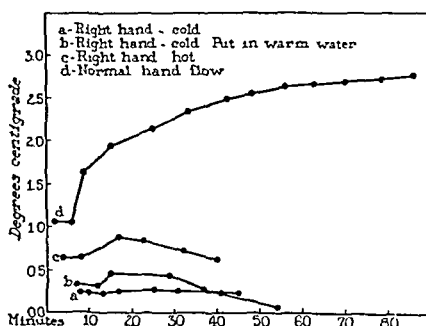


Figure 6. Calorimetric studies of the upper extremities in diabetes insipidus.

animal; the only curves of heat production comparable to these are those obtained in cases of Raynaud's disease. The gross appearance of the hands and the microscopic studies of the nail-fold capillaries also resemble the changes observed in Raynaud's disease. The underlying cause of the phenomenon in our patient was undoubtedly marked arteriolar spasm with capillary stagnation, and may be indicative of a compensatory mechanism to prevent the loss of heat from the body surface. The possibility that these disturbances of heat regulation may be due to water intoxication per se must be borne in mind for, as Greene and Rowntree have shown, this condition may cause a reduction in

body temperature. Our patient refused to tolerate an intake of warm water long enough for a detailed study of this point. Our previous experience with other patients suggests, however, that these vasomotor changes are due solely to the calorie requirements necessary to heat large quantities of cold water. The causal relationship of encephalitic changes to the vasomotor phenomena cannot be positively excluded, although a relation such as seen in this case has not, to our knowledge, been observed or described.

SUMMARY

In a case of severe diabetes insipidus secondary to epidemic encephalitis, the following unusual features have been observed:

1. A compulsion type of thirst relatively unaffected by pituitrin.
2. A history of convulsions, which on analysis appeared to be secondary to water intoxication.
3. Clinical evidence of such intoxication while the patient was under observation, accompanied by laboratory data suggesting blood dilution. These changes are similar in kind and degree to those accompanying experimental water intoxication.
4. A compensatory mechanism of heat regulation, to counterbalance the heat debt incurred by the ingestion of large amounts of ice-water. This mechanism included an increased intake of food to meet the excessive calorie requirements, muscular movements (shivering) and peripheral vasoconstriction producing phenomena similar to those observed in Raynaud's disease. These vasomotor changes appeared to be affected by pituitrin and the water balance at the moment.

The danger of pituitrin in such a case is obvious; with the kidneys rendered less active to an excess of water by the drug, the urinary output is reduced. Since the thirst was only slightly diminished, the possibility of blood dilution and consequent water intoxication is greatly increased.

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THE ACTION OF SUPRARENAL TISSUE UPON LECITHIN*

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Histological evidence suggests that the cortex of the suprarenal glands is closely associated with lipid and cholesterol metabolism, although it is not yet certain whether the function of the glands is concerned with the synthesis, storage or breakdown of these substances. In regard to the lipoids, there is some evidence that both synthesis and breakdown may occur; cholesterol does not appear to be synthesised but to be taken up by the suprarenal cortex from the blood-stream.

It was found experimentally that the incubation of dried suprarenal tissue with lecithin in a saline medium at pH 7.4 and at 37°C. was always followed by certain changes. The concentration of the lecithin used was 0.5 gms per 100 cc. of solvent and that of the suprarenal tissue was 0.1 gms. The saline solvent contained 0.6% NaCl, 0.2% NaHCO₃ and 0.1% glucose. After all the components had been added, carbon dioxide was passed in with frequent shaking until pH 7.4 was reached. The flasks were then sealed and incubated at 37°C. after the addition of a little chloroform.

Within forty-eight hours the fluid containing the suprarenal substance became milky, while the control was not much altered. After three days there was a separation of the fluid into a fairly clear upper layer and a markedly milky lower layer, while at this time a slight milkiness was developing in the control without any separation of the fluid into layers. This suggests that the presence of suprarenal tissue has accelerated a hydrolysis of the lecithin which was proceeding more slowly in the alkaline control fluid.

Using equal parts of lecithin and cholesterol these changes became more distinct. After four days' incubation the cholesterol in the control flask had come out of suspension as a white

* This work was carried out } under the Foulerton Committee of the Royal Society.

crystalline mass at the bottom of the flask. In the flask containing the suprarenal tissue the fluid was sharply divided into two layers, and at the bottom of the flask was an oily paste without crystalline structure and consisting largely of cholesterol esters. Other gland substances tested in a similar manner were thyroid, parathyroid, anterior and posterior pituitary and thymus. Of these none produced the characteristic milki-ness of the solution within forty-eight hours, while in four days the thymus alone appeared to have any pronounced action. It therefore seems probable that one function of the suprarenal gland is to hydrolyse lecithin and that the resulting fatty acids combine with cholesterol to form esters.

The hydrolysis of lecithin should lead theoretically to the liberation of choline, and the changes which have been described should be roughly indicated by the weight of choline mercurichloride recovered from the solutions. From the formula usually given, one gramme of lecithin should contain 156 mgm. of choline. As will be shown later, during the long period of incubation choline tends to be converted to some other substance, perhaps betaine or neurine, which gives considerably less than the theoretical yield of choline mercurichloride. After complete hydrolysis, one gramme of lecithin should yield about 780 mgm. of betaine mercurichloride. One would in any case expect a larger yield of mercurichloride from the fluid containing the suprarenal substance than from the control, and this was found to be the case:

Substrate	Mgm. Mercurichloride per 100 cc.	
	Control	Suprarenal
Leechithin only.....	21.2	44.0, 41.2
Lecithin and cholesterol.....	51	68.5, 79.6

In both cases the test fluid yielded more of the choline derivative than the control. It is also seen that the addition of cholesterol accelerated the rate of hydrolysis of the lecithin about equally in both solutions, so far as is indicated by the mercurichloride precipitate. The other gland substances mentioned above gave figures sufficiently near those of the control to suggest again that by comparison their action upon lecithin is comparatively slight.

It is noted, however, that although suprarenal substance appeared to accelerate the hydrolysis of lecithin, the yield of

mercurichloride was only about ten per cent of the theoretical. It seemed possible that the gland substance might have some action upon the choline so that its combination with mercuric chloride was prevented.

On incubating choline hydrochloride with suprarenal substance, it was found that a considerable reduction occurred in the amount of mercurichloride recovered from the test fluid, as compared with that recovered from the control. Incubation was carried out in the saline medium already described for four days at 37°C and pH 7.0. The fluid was then filtered, acidified, evaporated almost to dryness and extracted with alcohol. To the alcoholic extract a saturated solution of mercuric chloride in alcohol was added, and after standing the precipitate was filtered off, dried and weighed.

Theoretically one part of choline should form nearly fifteen times its weight of choline mercurichloride, and since the concentration of choline hydrochloride used was 20 mgm. per 100 cc. of solvent, the theoretical yield from the control should have been about 300 mgm. of choline mercurichloride. Assuming that a conversion to betaine occurs during incubation, then the yield would be about 100 mgm. per 100 cc. of fluid. The yield from the control flasks was usually of this order, but when suprarenal substance was present, it was always considerably less.

Mgm. Mercurichloride Recovered per 100 cc.		Gms. Suprarenal Substance Used per 100 cc.
Control	Suprarenal	
95	21	0.1
105	25	0.1
90	36.5	0.1
86	12	0.2
127	54	0.1 (ether extracted)

In the last instance the suprarenal substance had been extracted for a week with ether in a Soxhlet apparatus.

Although the method of recovery of the mercurichloride precipitate is admittedly a rough one, it indicates definitely that the presence of suprarenal substance has caused a decrease in the amount of the precipitate as compared with the control fluid.

On distilling the fluid in which suprarenal substance had been incubated with choline hydrochloride, formic acid was pres-

ent in the distillate in readily appreciable amounts. Oxalic acid did not appear to be present in the fluid.

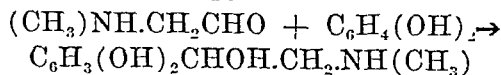
On evaporating the fluid to dryness, extracting with alcohol and boiling with cyanamide, positive colour tests for creatinine were obtained after the necessary treatment with hydrochloric acid.

COMMENT

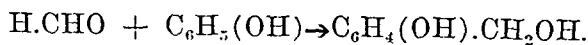
If choline hydrochloride is warmed in alkaline solution in the presence of an oxidising agent, trimethylamine is given off and oxalic acid is formed. If formic acid is to be produced through this type of reaction, it must be formed by a separation of the carbon atoms of the glycol group, a reaction which does not appear probable.

On the other hand, it is possible to conceive that the formic acid is produced by a process of demethylation of the nitrogen atom of the choline, leaving the glycol group intact. This would account both for the diminution of the mercurichloride precipitate, and also for the appearance of the formic acid. Although demethylation is considered to be a rare biological event, it is not unknown. It has been shown to occur in the case of the trimethyl- and dimethyl-purines, and it has been suggested by Riesser (1) as occurring in the formation of creatine through the condensation of choline and urea. It must also occur in the formation of guanidine from choline, as suggested by Paton (2). Further, Clément (3) has identified formic acid in the suprarenal glands.

Boruttau (4) suggested that the side-chain of the adrenaline molecule might be part of a choline nucleus, and if demethylation of choline occurs it is conceivable that methylaminoethanol will be a stage in its breakdown. In its aldehyde form this substance may combine with pyrocatechol:



to form adrenalin, as formaldehyde is known to combine with phenol in alkaline solution:



While it is admitted that the evidence for the formation of adrenalin from choline and pyrocatechol is slight, the chemical changes involved are simple, being those of oxidation and condensation as compared with the rather complex changes necessary

to transform tyrosine to adrenalin, a view which though generally accepted, has no experimental foundation. The present view is supported by the histological evidence of lipoid degradation, and since aminoethanol, the base of cephalin, can also be theoretically derived from choline, the occurrence of lipoid synthesis in the suprarenals may be accounted for. Finally it is known that the disappearance of lipoid granules from the cortex is accompanied by cessation of adrenalin output.

SUMMARY

1. Suprarenal gland substance causes a lipolysis of lecithin. In the presence of cholesterol this reaction is accelerated and cholesteryl esters are formed.
2. Suprarenal substance appears to attack choline. Formic acid is found in the distillate.
3. It is suggested that the side-chain of the adrenalin molecule may be derived from choline.

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VERTIGO AND DEAFNESS ASSOCIATED WITH HYPOTHYROIDISM* †

ROBERT C. MOEHLIG, M.D.

DETROIT

The association of deafness with hypothyroidism is fairly well known and this is particularly true of cretinism, where the incidence of deafness is remarkably high. It is not surprising, therefore, that we find symptoms referable to the semicircular canals and organ of hearing associated with hypothyroidism in adults. We have encountered many cases characterized by noises in the ear, attacks of dizziness which may be associated with vomiting and loss of consciousness, and progressive loss of hearing in patients suffering from hypothyroidism.

The following case illustrates the type we have encountered:

A woman of 36 complained that for one and a half years she has had spells of vertigo of such severity that objects would seem to spin around. Nausea and vomiting invariably accompanied the attacks, which usually lasted about one hour. They came at intervals of one to two weeks. It was necessary to lie down at the onset of the attack. The attack gradually wore off during the course of an hour, but during the intervals there was a constant buzzing and hissing in the right ear. She had lost the hearing of the right ear during the course of one and a half years. She tired easily.

The following findings in the physical examination were of importance: She was a woman of normal weight for her height of five feet four inches. She was totally deaf in the right ear. There was no other cranial nerve involvement. The thyroid gland was palpable. The skin was dry and she did not sweat very much even in hot weather. The extremities were cold. The nails were brittle. The basal metabolism was minus 28 per cent. The Barany test gave no reaction in the right ear. Blood pressure was 126/60. Other laboratory findings and roentgenological studies of the mastoid were normal.

She was placed on half a grain of desiccated thyroid extract three times a day and after two weeks noticed an improvement in her condition. She continued on this medication for four weeks until her basal metabolism was normal. Since that time she has taken smaller doses intermittently and has had no attacks during a course

*From the clinic of Drs. Ballin, Allen and Moehlig.

†Read at Eleventh Annual Meeting of the Association for the Study of Internal Secretions, Washington, D. C., May 17, 1927.

of nine months. She has no more dizziness, except mild attacks of vertigo. The deafness, of course, is uninfluenced.

The numerous etiological factors mentioned as producing Meniere's syndrome will not be discussed in this paper. I have encountered twenty-four cases of vertigo and deafness in patients with low metabolic rates. Of particular interest, as having a direct bearing upon the etiology, is the fact that some of our subjects had had partial thyroidectomy for toxic goiter, including the adenomatous and exophthalmic types, followed within a short time after operation by symptoms of hypothyroidism with a low basal metabolism. The incidence of hypothyroidism in these operative cases has been much higher since the operation for toxic goiter has become more radical. Alexander (1) in a recent three volume work devoted to neurology of the ear gives but brief mention of post-operative myxedema and ear noises. All operative cases developing vertigo had metabolic rates varying from twenty-five to sixty per cent above normal previous to operation, contrasting rather strikingly with a post-operative minus rate of eighteen to forty per cent.

The sex incidence in our series was sixteen females and eight males. The majority of non-operative cases in the female were around the menopause age.

As to the pathological changes present, we have had no opportunity to study the auditory organs of any of our cases. There are varying and diverse reports of the structural disorders found in the auditory organs in cretinism and myxedema. Otospongiosis and otosclerosis are reported by some. The reports from the otologists who studied our cases were that the patients suffered from nerve deafness and that they had a delayed response to stimuli in the affected ear.

The duration of symptoms ranged from two months to six years, the shortest duration being in those individuals in whom we recognized the symptoms soon after operation, and in those who had come to us since our attention was called to this type of association. The attacks would come on at intervals of one to two weeks and would make the individual intensely sick; vomiting usually accompanied the attack. At times fainting would also occur and it invariably caused such intense vertigo that support was necessary. The duration of the attacks was from a few minutes to two hours. Buzzing, ringing in the affected

ear, described frequently as like hissing steam, was constantly present between attacks. We never found that both ears were involved.

It was surprising to note that despite the very low basal metabolism but few cases showed any striking hypothyroid signs. We consider this important because, for this reason, the association is not thought of. Dryness of the skin, lethargy, lack of memory, fatigue and cold extremities were the usual complaints in the severer grades of hypothyroidism. There was no marked obesity in any of our cases, but in some of the surgical cases the gain in weight after operation was quite rapid, though not excessive.

All the patients had either a normal or subnormal blood pressure. Some of the operative cases had had high blood pressure previous to, but were normal or subnormal after operation.

Laboratory findings, other than the low metabolism, were normal. The x-ray findings of the mastoids were also negative. The Barany test gave no reaction on the affected side in those cases which had gone on to total deafness. There was no other cranial nerve involvement.

Barlow (2) in studying the vestibular nerve function in fifteen cases of myxedema concludes that there is a definite clinical vestibular picture which can be demonstrated by the equilibration tests and is in the nature of a delayed response to stimuli; furthermore, that there is no relationship between the basal metabolic rate and the degree of this retardation.

In one case in which he was able to test the effect of thyroid therapy, improvement in response to stimuli was noted, and suggests the possibility that this clinical picture may be improved by thyroid extract. The improvement noted in hearing in eighteen of our cases which had not gone on to total deafness would bear out Barlow's suggestion.

Treatment consisted of desiccated thyroid extract in sufficient dosage to bring the basal metabolism to normal, and then the dosage was reduced to maintain the normal. Marked improvement was noted in the vertigo symptoms and practically all had but very mild attacks following this form of treatment. Spells of vertigo were present occasionally. The deafness was, of course, not improved, but I am led to believe that in some of the early cases we have prevented the development of deaf-

ness. The benefit derived from the thyroid extract was so marked that there hardly seems to be any question as to its efficacy. Outstanding is one case—that of a nurse with symptoms of one and a half years' duration. Her symptoms were very suggestive of a cerebello-pontile tumor. She showed immediate improvement on one-half grain (0.33 mgm.) of desiccated thyroid t. i. d. She continued this for three weeks and for seven months has been taking it sporadically. Some of the cases with very low rates have been taking it continuously.

Some of the conditions with which this syndrome may be confused are cerebello-pontile tumors, migraine, labyrinthitis, and syphilis. In the tumor cases, differentiation of a well developed case should offer no trouble, as there are present headache, choked discs (missing at times, of course), nystagmus and involvement of other cranial nerves. The basal metabolism is not affected. In early cases confusion is quite possible, but the therapeutic test is also helpful.

Differentiation from migraine offers less difficulty. While migraine symptoms are similar to the syndrome mentioned, nevertheless there is present headache, which the individuals afflicted with this vertigo do not usually have. Likewise, there is no difficulty in the hearing, nor is there any disturbance in the basal metabolism and a familial tendency is often present.

Given a case of vertigo, with or without vomiting or fainting spells, ringing and buzzing in the ear, lessened or absent hearing, low or normal blood pressure, and a low metabolic rate, in the absence of striking hypothyroid signs, we are justified in the conclusion that we are dealing with a unique and characteristic symptom complex heretofore not appreciated as a clinical entity, and that the exhibition of thyroid in these cases may be expected to result in marked relief or complete cure.

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THE EFFECT OF PREGNANCY AND LACTATION ON THE BLOOD CALCIUM OF THYRO-PARATHY- ROIDECTOMIZED DOGS

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In our previous work (Fisher and Larson, 1925) we have shown that a decrease in the calcium of the blood serum invariably accompanies the onset of tetany in a thyro-parathyroidectomized dog. The work of MacCallum and Voegtlin (1909), Salvesen (1923) and Hanson (1924) was not entirely accepted by Dragstedt, et al. (1924).

The methods used in preparing potent parathyroid extracts and in operating upon the dogs were those reported in a previous paper (Fisher and Larson, 1925). The dogs were purposely kept on a meat diet. The calcium values are all of the blood serum and are given in terms of 100 c.c. of blood serum. All determinations were made in duplicate by the method of Clark and Collip (1925).

Protocol, Dog A. Female Collie. Weight, 13 kgm.

March 12, 1925—Thyro-parathyroidectomy performed.

March 15-22—Markedly depressed.

March 25—Appetite fair. Condition good.

March 26—9 p.m. Tetany. 5 cc. extract given.

March 27—Ate greedily. Placed in pen with other dogs.

May 6—Removed from general pen.

May 7—Gave birth to 5 pups.

June 9—Blood calcium. 8.22 mgm.

June 18—Blood calcium. 7.56 mgm.

July 9—Blood calcium. 10.80 mgm. Weaned pups.

July 9, 1925, to August 19, 1926—Condition good. The blood calcium values varied from 9.5 to 11.08 mgm. Twelve samples were analyzed at regular intervals during this period. At the end of this period a careful autopsy was performed but no parathyroid tissue was found.

234 PREGNANCY, LACTATION AND BLOOD CALCIUM

Protocol, Dog B. Female Shepherd. Weight, 14 kgm.

June 13, 1925—Thyro-parathyroidectomized.

June 15—Impending tetany. 6 cc. extract injected.

June 16—Severe tetany. 8 cc. extract injected.

June 19—Severe tetany. 10 cc. extract given. Complete recovery.

July 8, 1925, to January 28, 1926—Ten blood calciums at regular intervals varied between 9.28 and 11.05 mgm.

March 27, 1926—Animal pregnant, near term. Blood calcium 7.22 mgm. Some evidences of tetany such as hyperpnoea, but no injection was made.

March 30—Blood calcium 7.69 mgm.

March 31—Blood calcium 8.40 mgm. Gave birth to 9 live pups.

April 2—Blood calcium 9.70 mgm.

April 3 to May 21—During this period 5 blood calcium determinations varied between 9.55 and 10.25 mgm.

July 23—Refused food.

July 24, 1926—8 a. m. Animal dead. Body heat present.

Autopsy. Important findings. Mass of hair 10 cm. in diameter in pyloric end of the stomach. Broncho-pneumonia in middle and lower lobes of the right lung. Two glands in the neck region, the one located on the right side at the level of the cricoid cartilage 1 cm. in diameter, the other 2mm. in diameter in the midline of the neck, midway between the cricoid cartilage and the upper border of the manubrium sterni.

Microscopic examination. The larger gland was lymphoid tissue. The smaller gland was parathyroid tissue.

DISCUSSION

From the data presented it is evident that there is a decrease in blood serum calcium during pregnancy and lactation. In the case of Dog A the calcium analyses were not made until nearly a month after the birth of the pups. Even at this time, which was near the end of the lactation period, the calcium was near the tetany level. Within a month after the pups were weaned the calcium returned to a normal level. In the case of Dog B, in which the calcium of the blood was determined at more frequent intervals, it was shown that the calcium decreased gradually, almost to the tetany level as pregnancy advanced. There was a rapid return to normal following delivery.

These results suggest that during lactation and pregnancy such demands are made on the calcium supply of the body that the blood calcium level is markedly changed even in the presence

of at least one accessory parathyroid gland. Hanson (1924) has shown that it is possible to produce tetany in pregnant bitches by removal of only the external parathyroids.

These results are not in agreement with those of Dragstedt, et al. (1924). The analyses reported by this investigator vary from 9.3 to 10.4 mgm. per 100 c.c. of blood. These values are within normal limits for blood serum. It is not stated whether the values are of the serum or whole blood. The method used (Clark, 1921) is applicable to whole blood, serum or plasma. For whole blood the values are much too high. However, values like 9.3 mgm. per 100 c.c. in the case of a dog dying in tetany are inconsistent with the findings of Collip (1925) and Fisher and Larson (1925), where an improved method for calcium determination was employed.

Both of our animals showed that during pregnancy and lactation there was a marked decrease in the calcium of the blood serum in spite of the fact that some parathyroid tissue was found at autopsy in the one dog. We believe there was accessory parathyroid tissue in Dog A. These dogs did not experience many severe attacks of tetany, even though they were fed on a meat diet. The tetany was easily controlled, and in a short time parathyroid extract was not necessary. The calcium level returned to normal and remained constant. The superposing of pregnancy and lactation on the condition of parathyroid deficiency, when the animals were on a meat diet, caused a marked decrease in the blood calcium level. When the demands on the calcium were removed, there was a return of the blood calcium to normal.

SUMMARY

In two cases it was shown that pregnancy and lactation were accompanied by a decrease in the blood calcium of thyroidectomized and partially parathyroidectomized dogs that had maintained a normal calcium level preceding pregnancy.

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236 PREGNANCY, LACTATION AND BLOOD CALCIUM

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A CASE OF RETINITIS PIGMENTOSA ARRESTED BY ORGANOTHERAPY AND ANTISYPHILITIC TREATMENT*

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The term "retinitis pigmentosa" is misleading, but since it has been long in use it is employed in this communication. De Schweinitz's suggested designation, "pigmentary degeneration" of the retina, might be better. Collin's and Wilmer's term, "retinal abiotrophy," is more descriptive. In view of the grave disposition in this disorder to total and permanent blindness, it is believed that a preliminary report of an arrested and improved case will be of interest, especially since an older brother and sister of the patient are in the school for the blind, from the same cause. These are all quite typical cases with abiotic degeneration of the retina, the thread-like contraction of the blood vessels, pigment deposits, increasing contraction of the visual field, and progressive blindness. The particular interesting thing about the case reported, especially as to diagnosis, is that the sella turcica was seen to change radically under observation, clearly showing pituitary disease.

Consanguinity is a feature, though rather remote, the great grandparents on the father's side having been first cousins. There is no history of impaired vision on either side of the family. No history of syphilis can be traced and the Wassermann reaction is negative.

The patient was extremely small at birth. The mother's father had heart disease that might have been syphilitic. The mother's brother had a child afflicted with "glandular trouble," but who got well. The father's brother had a son born physically defective and not walking until three years of age. Syphilis

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crept into the blood somewhere down the line. We are convinced from our experience in numerous cases of eye disease that a negative Wassermann test should be disregarded. From a large experience in diseases of the eye, we are compelled to conclude that inherited syphilis is at the bottom of many of these cases, even though the indications may be negative. This disease seems to have special affinity for the pituitary body, the structures about the third ventricle, and for the eye, as well as the other structures coming from the ectoderm. We are convinced that there is a syphilitic blood state of great importance indeterminable by present laboratory methods.

It should be said that while the cases herein mentioned were all typical, there was but slight nystagmus, no strabismus, nor any mental deficiency. The three children are all very bright and are making high marks in school. The first two cases are reported for comparison and to show the familial tendency. There are no other children in the family. Our information concerning these two children is rather limited, except as to the present state.

CASE I. W. J. C., aged eighteen, male. There is no history of serious infectious disease or important illness of any kind. Development was normal and he is now physically sound. Impairment of vision began at six. A skiagram made on July 22, 1922, revealed the sella turcica to be of the deep saddle type with clinoid processes closed and pressing upon the pituitary body. Progressive blindness compelled him to begin residence in a school for the blind at twelve. No glandular or syphilitic basis was recognized nor was much treatment given since the case was believed to be hopeless.

CASE II. E. M. C., aged fifteen, female. The history of this patient is quite similar to that of the older brother. She gave no history of infection or serious illness. Her development was normal. Mentally she is very bright. Trouble with the vision began at eight and progressed steadily. She entered a school for the blind at fourteen. July 22, 1922, x-ray examination revealed a sella turcica of the dish type with over-development, clubbing and closing of the posterior clinoid processes, with great pressure. Possible syphilitic inheritance and pituitary basis of the trouble was not considered. No special effort was made in treatment, as it was thought nothing helpful could be done.

CASE III. R. A. C., aged nine, male. The patient weighed four pounds at birth and developed slowly. Mentally he is very keen and is making high grades at school. A series of important infectious diseases occurred, including a severe attack of influenza at six and pneumonia and scarlet fever with nephritis later. There has been no

post-nasal bleeding, epileptoid spells, or vomiting; no polyuria, nystagmus, strabismus or diplopia; no pain, no night blindness. X-ray examination (Richardson) made as a precaution at six, July 22, 1922, showed a normal sella turcica. At this time the health was good. Three years later vision was impaired and the sella was found decidedly abnormal. After two months, September 15, 1925, when vision was much worse, another picture showed marked clubbing of both clinoid processes with serious encroachment on the pituitary body.

Examination showed the patient to be undersized and unhealthy in appearance, poorly nourished with flabby muscles, thin and anemic looking. The blood pressure was 70/50. The blood examination showed: Hemoglobin, 65 per cent; red blood cells, 4,000,000; leucocytes, 7,800. A differential count showed: polymorphonuclear leucocytes, 53 per cent; lymphocytes and mononuclear cells, 36 per cent. The phenolsulphonphthalein test gave 75 per cent recovered in two hours. The alveolar air test gave 25 mm. The bones were small, the hands narrow and tapering and the skin very smooth and dry—all suggestive of pituitary insufficiency. The adrenal white line was a prominent feature. Bust, hips and legs were decidedly of the feminine type. The sex organs were not properly developed. The biceps, epigrastric, umbilical, cremasteric, and knee reflexes were all greatly exaggerated, which would seem to be unusual. Examination of the urine showed absence of sugar, albumen, casts, and red blood cells. No evidence of focal infection was found; x-ray examination showed the sinuses to be clear. A calcium deficiency was indicated by a tendency to marked kyphosis. The color vision was apparently normal, except for some doubt about green. Vision was 5/200 minus.

It was suspected that there was a syphilitic inheritance at the basis of the condition, and it was certain there was pituitary disease. The patient, accordingly, was put on glandular therapy, chiefly pituitary, but including adrenal and thyroid, according to indications, together with the old mixed treatment for syphilis, namely, mercury, iodide, nux vomica, and iron. A full vitamine diet was prescribed. The improvement was prompt and marked.

After six months' treatment, the patient had grown two inches, had gained nine pounds in weight and the general condition was excellent. The blood pressure was up to normal, 95/60. The hemoglobin was 82 per cent; the red blood cells, 4,500,000; the leucocytes, 7,200. The differential count showed polymorphonuclear leucocytes 66 per cent and lymphocytes and mononuclear cells 34 per cent. The "Pthalein" test gave 95 per cent recovery. The alveolar air had increased to 40 mm. The kyphosis was much corrected and the endocrine func-

tions seemed much better. The patient was now developing rapidly and was in fine condition mentally and physically.

At this time the retention in vision was surprising: the retina had cleared very much; the spots had faded perceptibly and scar tissue appeared to have taken the place of the pigmentary deposits. Unquestionably the condition of the eye grounds was materially better, indicating that the disease was probably arrested.

It is sufficient in concluding this report two years later, to say that the improvement of vision has been maintained and is now 12/200.

Abstract Department

Importance of creatine, creatinine, and arginine in adrenalin action (Über die Bedeutung des Kreatins, des Kreatinins und des Arginins für den motorischen Effekt des Adrenalins). Brodd (C. A.), Skand. Arch. f. Physiol. (Leipz.), 1927, 50, 97-154; Abst. Physiol. Absts., 12, 116.

In perfusion of the blood vessels of the eviscerated frog by Göthlin's fluid, creatine in a concentration of 0.001% increases the flow, but in this or less dilution enhances the constrictor action of adrenalin. Creatinine in 0.05% solution dilates the vessels, but does not influence adrenalin action, while arginine in 0.0003% solution facilitates adrenalin constriction. Neither creatine, creatinine, nor arginine has any action alone on the rabbit's uterus, and of these only arginine appears to facilitate the effect of adrenalin on the uterus.

Experimental research on the influence of adrenal cortex on body growth. Castaldi (L.), Rev. sud-americana endocrinol. immunol. quimioterap., 1926, 9, 861-879; Abst. Chem. Absts., 21, 953-954.

Biometric, clinical and laboratory experiments prove that the adrenal cortex and not the medulla promotes body growth by a morphogenic hormone produced in its cells. Since the effect is less than that of the thyroid and of the hypophysis, possibly even less than that of the thymus, the admixture of large proportions of adrenal in pluriglandular preparations employed in growth deficiencies is not justified. Cortex alone should be used in view of the antagonistic and harmful effect of adrenaline in continued use.

Pharmacological effect of ephedrine. Kreitmair (H.), Arch. f. exper. Path. u. Pharmacol. (Leipz.), 1927, 120, 189-228; Abst. Chem. Absts., 21, 1498.

The effects of ephedrine were analyzed through study of its action on blood pressure, heart action, on the vessels, on the respiratory center and on the bronchi, on the pupils, the intestine and the uterus, on the secretory activity of glands and on the blood sugar. Blood pressure is increased by small doses, lowered by large doses. Heart action is stimulated by small, inhibited by large doses. The blood vessels are constricted. Small doses stimulate the respiratory center and dilate the bronchi. Pupils are dilated. The action

of intestinal muscle is inhibited by small doses more than by larger ones. Any effect on glandular secretion is masked by the effect on the vessels. Ephedrine causes but little change in the blood sugar. The toxicity is not high. Ephedrine is destroyed in the body much more slowly than is adrenaline, and its effects persist for a correspondingly longer time. It is relatively insusceptible to the digestive fluids, does not deteriorate quickly and can be sterilized.

Spectrophotometric study of adrenaline, Lopez (J. M.), *Anales soc. cient. Argentina*, 1926, **101**, 133-154; *Abst. Chem. Absts.*, **21**, 1129.

The ultra-violet spectra of natural and synthetic adrenaline-HCl are identical. The maximum absorption is 2780. The method is suitable for the determination of adrenaline.

Study of epinephrine. Maxenchs (A. T.), *Ars Medica (Barcelona)*, 1927, **3**, 1; *Abst. J. Am. M. Ass.*, **88**, 1609.

Maxench's experiments on dogs apparently show that epinephrine by mouth causes a transitory increase in blood sugar. This increase is proportional to the dose. The drug should preferably be given on an empty stomach. When given orally, five to ten times as much epinephrine is required as when it is injected. As toxicity is almost nil when it is given by mouth, the drug can be used concentrated in an isotonic solution, either Ringer's or a sodium chloride solution.

Does adrenaline exist in a totally free state in fresh suprarenal capsules? Mouriquand (G.) & Leulier (A.), *Compt. rend. Soc. de biol. (Par.)*, 1926, **183**, 1353-1355; *Abst. Chem. Absts.*, **21**, 954.

Guinea pigs in series of 6 each were killed and the suprarenals were removed as quickly as possible. These were divided into two lots, A and B, made up of equal numbers of right and left glands. Both lots were weighed immediately, and A was ground with anhydrous Na_2SO_4 to a powder, was allowed to macerate 30 minutes, when it was tested for adrenaline by the method of Bailly. B was placed in a vacuum desiccator with H_2SO_4 and after 24 hours was tested for adrenaline by the same method. A showed a faint trace of adrenaline; B gave from 0.15 to 0.26 gm. of adrenaline per kgm. of fresh material. Apparently adrenaline does not exist totally free in more than traces of the suprarenals.

Gases of the blood in suprarenal insufficiency. Pico (O. M.) & Deulofeu (V.), *Compt. rend. Soc. de biol. (Par.)*, 1926, **95**, 1505; *Abst. J. Am. M. Ass.*, **88**, 1118.

The authors made observations on suprarenalectomized dogs. The oxygen capacity of the blood increased, probably in connection with concentration of blood corpuscles. Saturation of the venous

blood with oxygen decreased, owing, presumably, to reduction in the volume of the blood and to slowing of the blood stream. The carbonic anhydride diminished, especially in the arterial blood, because of hyperpnea. The changes in the blood resemble those described by Henderson in shock, which result finally in acapnia.

Comparative variations in the content of the suprarenals in water, fatty acids and cholesterol in the normal guinea pig, and in the guinea pig under a diet deficient in the antiscorbutic vitamin. Randoin (L.) & Michaux (A.), *Compt. rend. Soc. de biol. (Par.)*, 1926, **183**, 1055-1057; *Abst. Chem. Absts.*, **21**, 1139.

In the adult normal guinea pig the suprarenals contain an average of 5.9 gm. of cholesterol per 100 gm. of fresh organ when on a natural diet and 5.07 gm. with a complete artificial diet; they contain 8.87-8.83 gm. of fatty acids and 68.9-68.4 gm. of H₂O per 100 gm. of fresh organ. On a diet deprived of the antiscorbutic vitamin the cholesterol content falls and toward the end reaches 2.63-2.78 gm. per 100 gm. The fatty acids diminish at the beginning, then become normal and even greater than under a complete diet. The water content remains about constant.

Diagnosis of primary suprarenal tumors. Schmieden (V.) & Peiper (H.), *Arch. f. klin. Chir. (Berl.)*, 1926, **143**, 491; *Abst. J. Am. M. Ass.*, **88**, 1610.

Five cases of primary tumor of the suprarenal body are described, one a blood cyst in a child 5½ months old. In the three cases in which it was employed, pneumo-peritoneum led to correct diagnosis, either with certainty or great probability. The authors consider it of the greatest value in the diagnosis of these tumors. By control of the vascular supply in situ the origin of the tumor in the suprarenal body may be determined during operation. Precocious puberty is seen in children, sex inversion in women with carcinoma of the cortex. Crises of pain are occasioned by pressure of suprarenal tumor on the thoracic or lumbar nerve roots. Bronzing of the skin is a not unusual symptom. Hematuria may be present.

The influence of the thyroid and of insulin on the oxydases in different organs. Mori (K.), *Folia Endocrinologica Japonica (Kyoto)*, 1927, **2**, 40-41.

Studies were made on the influence of the thyroid and of insulin on the oxydases in the heart, the liver and the kidney, employing the histological method of Gierke and Gräff and the chemical method of Vernon. In the normal rabbit, the heart possesses a more marked oxydizing power than the kidney and liver. Insulin injected into the veins of the normal rabbit produces a slight augmentation of the oxydase reaction. This augmentation is greater

in the heart than in the kidney and is inconstant in the liver. The combined injection of glucose and insulin in the normal rabbit produces a marked augmentation of oxydase reaction. Consequently, although insulin alone can stimulate the intercellular oxidation, an increase of the amount of glucose in the tissues causes a greater effect. By histological examination the intravenous injection of thyroid extract causes a marked augmentation of the oxydases in all organs. But according to chemical examinations the results are positive only in the heart and kidney; they are indefinite in the liver. The simultaneous injection of insulin and of thyroid extract produces a striking augmentation of the oxydases by histological examination. In this case the augmentation is greater than the total of the two augmentations given by the separate injections. By chemical examination the augmentation in the heart and the kidney alone is a little greater than that in the case of the two separately made injections; in the liver it is indefinite. All the organs in the rabbit submitted to the thyroid treatment are richer in oxydase than those of the controls. The injection of insulin in the hyperthyroid rabbit produces a marked augmentation in all organs. The ablation of the thyroid provokes a diminution of the oxydases in all organs; the intravenous injection of insulin in the thyroidectomized rabbit produces a slightly smaller augmentation of the oxydases than in the normal rabbit. That is to say, the decrease of intercellular oxidation produced by thyroidectomy is compensated for by the injection of insulin at the normal level or a little above. The conclusion is made that there exists a synergism between the thyroid hormone and insulin as to the quantity of the oxydases of the tissues.—R. R. Durant.

Histological modifications in ovarian grafts (*Le modifichie istologiche dei trapianti ovarici negli animali*). Calvanico (R.), Internat. Rass. di Clin. e Terap. (Napoli), 1926, 7, 19.

The progressive histological changes in ovarian grafts were studied in an attempt to determine whether the interstitial gland or the germinative tissue is source of a hormone in ovarian transplantation. Forty female dogs and 10 female goats were used. The grafts were severally examined after 1 week, 10 days, 20 days and 40 days. The conclusion reached is that the ova and the germinative tissue are the first to disappear: that the interstitial gland, while lasting longer, undergoes some definite changes, which clearly show its relation to the reticulo-endothelial system.—G. V.

Castration in bats (*Les effets de la castration chez les chéiroptères*). Courrier (R.), Compt. rend. Soc. de biol. (Par.), 1926, 91, 1268; Abst. Physiol. Absts., 12, 117.

In bats, after castration in December, the accessory glands (prostate, etc.) remain unchanged if the animals are kept at a low

temperature hibernating, but undergo involution if the outside temperature is raised to 20° C.

Sex hormone from placenta ["feminin"] (Beitrag zur Kenntniss eines Sexaulhormons der menschlichen Placenta). Glimm (E.) & Wadehn (F.), *Biochem. Ztschr. (Berl.)*, 1926, **170**, 3-18; *Abst. Physiol. Absts.*, **12**, 116.

Preparation of a sex hormone from placenta by ether extraction is described. The increase in weight of the virgin rabbit uterus within a few days of the administration of the hormone is a useful qualitative test of the activity of preparations; 5 to 10 mouse units have a detectable effect, and 0.1 to 0.2 mgm. of the dry preparation corresponds to 1 mouse unit, 500 to 1,000 units being obtained from 1 kgm. of placenta. The presence of two hormones, one causing growth of the uterus and the other effecting the oestrus cycle, was not confirmed. Some activity was demonstrated in extracts of corpus luteum, but not in other tissues. The hormone may be administered orally or subcutaneously, the latter method being more effective. Large doses of the impure hormone damage the male generative organs.

The ovarian hormone (Zur Kenntnis des Ovarialhormons). Hartmann (M.), *Klin. Wchnschr. (Berl.)*, 1926, **5**, 2152-2154; *Abst. Physiol. Absts.*, **12**, 116.

The author describes the method he has used in an attempt to isolate the ovarian hormone from the extract obtained by Frankel and Herrmann's method. After removal of several inactive fractions, the residual substances were distilled in a high vacuum (boiling point about 185° C.). The distillate was very active. On saponification it gave a number of unsaturated fatty acids of the C₁₈ series. These were all inactive, but an unsaponifiable fraction still possessed considerable activity. In high vacuum it boiled at 145° C. and contained: C, 81.65 to 82.00%; H, 11.11 to 11.75%. It was unsaturated, but its structure has not yet been determined.

Histological changes in the testis of the guinea pig during scurvy and inanition. Lindsay (Blanche) & Medes (Grace), *Am. J. Anat. (Balt.)*, 1926, **37**, 213-236; *Abst. Chem. Absts.*, **21**, 945.

A diet deficient in vitamin C, or a diet containing sufficient A, B and C, but inadequate in total amount of food, both lead to degeneration of the seminal epithelium, unaccompanied by any marked change in the intertubular tissue. In young guinea pigs lack of C also retards development.

Emmenagogue action of the ovarian hormone. Loewe (S.), *Klin. Wchnschr. (Berl.)*, 1927, **6**, 59; *Abst. J. Am. M. Ass.*, **88**, 1362.

Loewe points out that the ovarian hormone promotes only the

building up of endometrium. Menstruation, which is the destructive phase, is due to cessation of this influence. Therefore the therapeutic administration of the hormone should be interrupted periodically to obtain an emmenagogue effect. Some cases of amenorrhea might be due perhaps to overproduction or overdosage of the hormone—rather than to its absence. The commercial preparations contain too little hormone to be active in castrated women. About 2,000 mouse units would have to be injected daily to obtain an effect. In mere hypofunction of the ovaries, smaller doses (perhaps 100 units) might help.

A lipo-gel reaction exerted by follicular fluid upon spermatozoa and its significance (Lillie's Reaction). Popa (G. T.), *Biol. Bull. (Lancaster)*, 1927, 52, 223-237.

When sperm suspensions are injected with follicular fluid taken from Graafian follicles, a coagulation is secured. The reaction is not produced by other liquids of the body, and is interspecific.

—M. O. Lee.

The corpus luteum in the hen and in mammals. Ramírez (E.), *Revista Mexicana de Biología (Mexico City)*, 1926, 6, 205; *Abst. J. Am. M. Ass.*, 88, 1120.

From an extensive study of the brooding hen, Ramírez concludes that the pregnant condition in mammals is already outlined in the hatching of birds. Brooding hens also possess a true homologous corpus luteum. Physiologic research of this type on birds would seem a promising field.

Ovarian hormone and the genitalia (Ovarialhormon, Wachstum der Genitalien, sexuelle Frühreife). Zondek (B.) & Aschheim (S.), *Klin. Wchnschr. (Berl.)*, 1926, 5, 2199-2202; *Abst. Physiol. Absts.*, 12, 118.

The water-soluble, dialysable hormone, prepared by the authors from ovary and placenta, and named "folliculin," has now been shown to produce growth of the uterus in immature mice. The average weight of the genitalia of mice treated for 14 days was 81 mgm., compared with 20 mgm. for control animals. The hormone also excites oestrus, and this condition is maintained so long as the hormone is administered. It does not produce maturity in the ovaries of immature mice, nor does it give rise to increased growth of the bones.

Action of pituitary extract on metabolism. Castex (M. R.) & Schteingart (M.), *Compt. rend. Soc. de biol. (Par.)*, 1926, 95, 1512; *Abst. J. Am. M. Ass.*, 88, 1118.

Castex and Schteingart administered extract of the posterior pituitary lobe to two healthy persons, to six patients with disease

of the thyroid, to two with disease of the pituitary, and to one diabetic patient. In ten, the basal metabolism increased; in one instance the increase was 27%. The metabolic changes were more pronounced in persons with a thyroid disturbance than in healthy persons. In patients with pituitary insufficiency the basal metabolism remained sometimes unaffected.

Hypophyseal colloid and cerebro-spinal fluid (*Colloïde hypophysaire et liquide cephalo-rachidien*). Collin (R.), *Compt. rend. Soc. de biol. (Par.)*, 1926, 95, 107; *Abst. Physiol. Absts.*, 12, 115.

Histological evidence from the duck that colloid passes from the posterior lobe of the pituitary through the infundibulum and the ependyma into the cerebro-spinal fluid in the infundibular recess.

Diabetes insipidus. Depisch (F.) & Högler (F.), *Wien. Archiv. f. innere Med. (Berl.)*, 1927, 13, 509; *Abst. J. Am. M. Ass.*, 88, 1528.

Five cases of diabetes insipidus fit into neither the hyperchloremic nor the normochloremic type. Pituitary extracts proved beneficial in all cases.

Changes in the pituitary after section of the right vagus. Eaves (E. C.) & Clark (G. A.), *J. Physiol. (Lond.)*, 1926, 62 (Proc.) i.

A preliminary communication based on the possibility that tonic inhibitory fibers to the islets of Langerhans exist in the right vagi of rabbits. After vagotomy, the pituitary was increased in size with histological changes similar to those occurring after insulin injection. It is suggested that these changes are due to increased insulin production occurring after removal of tonic inhibition.

—C. I. R.

Studies on the anterior lobe of the pituitary body. Johns (W. S.), O'Mulvenny (T. O.), Potts (E. B.) & Laughton (N. B.), *Trans. Roy. Soc. Can.*, 1926, 20, Sect. V, 243-245.

Protein-free aqueous extracts of ox anterior pituitary gland, from which the intermediate and posterior part had carefully been removed, when injected into healthy dogs produced hyperglucemia, glucosuria and polyuria. Intravenous injections into dogs and rabbits produced a slight rise in blood pressure. Successive injections always produced pressor effects. No effect was produced on rabbit- or guinea-pig-uterus strips, indicating that the active substance is different from those from the intermediate and posterior portions of the pituitary.—A. T. C.

Effect upon the intestine of extract of the posterior lobe of the hypophysis. Kaufmann (Margot), *Arch. f. exper. Path. u. Pharmacol.* (Leipz.), 1927, **120**, 324-329; *Abst. Chem. Absts.*, **21**, 1498.

Extracts of the posterior lobe which are free of histamine have but a very slight stimulating effect on the small intestines of the rabbit or cat. The ileum reacts more strongly than the jejunum. On the large intestine an inhibitory effect is manifest, and the inhibiting substance is destroyed by alkali. This inhibition is but transitory with low concentrations, and is followed by stimulating action. The active substance is present in the pars intermedia and in slight amounts in the pars neuralis. Apparently it is not identical with the substance which increases the blood pressure, stimulates the uterus or functions as an antidiuretic.

The pituitary gland and cholesterol metabolism. Moehlig (R. C.) & Ainslee (Harriet B.), *Ann. Clin. Med.* (Balt.), 1927, **5**, 772-779.

The authors believe that the pituitary gland regulates cholesterol metabolism and the tissues of mesenchymal origin. Arteriosclerosis, hypertension, certain types of nephritis, disturbances in blood volume, cholelithiasis, diabetes and uterine fibroids are found to have important relation to states of pituitary hyperfunction and hypofunction.—M. O. Lee.

Posterior pituitary extract and cholesterol metabolism. Moehlig (R. C.) & Ainslee (Harriet B.), *Am. J. Physiol.* (Balt.), 1927, **80**, 649-651.

Pituitary extract was injected in 1 cc. doses into 20 rabbits for a period of ten days. The blood cholesterol was increased in 17 of the 20 cases. The average for the whole series was about 31% higher after than before the injections.—R. G. H.

The effect of pituitrin on blood sugar. Tingle (C. D.) & Imrie (C. G.), *J. Physiol.* (Lond.), 1926, **62**, (Proc.) ii-iii. A preliminary report.

In a case of diabetes insipidus three subcutaneous injections of 0.5 cc. of pituitrin resulted in an increase in blood sugar, in each instance, of more than 100% in a half hour with return to normal in 2 to 3 hours. This effect is greater than that from 50 gm. of glucose. The fasting level of blood sugar in the patient was below the average. In normal subjects similar but less pronounced effects were obtained, except that after return to the initial level blood sugar continued to fall after one and one-half hours but rose again at the end of 3 hours. Pituitrin with glucose caused a rise of about 150% in an hour with return to the initial level in 2 hours, but a fall below normal thereafter. Pituitrin given an hour after glucose

produced approximately the same results. Pituitrin followed in a half hour by glucose gave results suggesting that the pituitrin effect occurred at once, the glucose effect somewhat later. The authors suggest that when blood sugar is raised, the pituitrin effect is delayed until it begins to fall again. In three cases of diabetes mellitus, pituitrin caused a fall in blood sugar in a half hour with return to the original level in 2 to 3 hours. No increase occurred in these cases.—C. I. R.

Changes in composition of blood in pernicious anemia. Murphey (W. P.), Monroe (R. T.) & Fitz (R.), J. Am. M. Ass. (Chicago), 1927, **88**, 1211-1214.

Changes were noted in the composition of the blood in ten patients with pernicious anemia, treated by a diet rich in liver. The results corroborate Minot and Murphy's observations that under proper dietetic care a prompt, rapid and distinct remission of the anemia is produced in each instance. The diet appeared to cause the delivery of new, young red blood cells from the bone marrow into the general circulation, as evidenced first by a prompt increase of the reticulocytes in the circulating blood. At about the time that there was evidence of a marked reaction in the bone marrow, there was a decrease of bile pigment concentration in the serum, as manifested by a fall in the icteric index. Coincidentally there was an increasing red blood cell count and hemoglobin concentration, accompanied by a progressive growth in the blood tissue as a whole, as estimated by blood volume determinations. The morphologic appearance of the red corpuscles under treatment became normal, or essentially so; the color index finally became 1 or less than 1; the average cell volume diminished and approached normal; the volume index and the "stroma" index became normal. The diet did not produce changes in the nonprotein nitrogen of the plasma or in the plasma protein. The protein of the corpuscles, however, increased notably, and in almost direct proportion to the increasing hemoglobin concentration.—Author's Summary.

Diabetic acidosis with negative ferric-chloride reaction in urine. Appel (K. E.) & Cooper (D. A.), Am. J. M. Sc. (Phila.), 1927, **173**, 201; Abst. J. Am. M. Ass., **88**, 1597.

An analysis was made of the records of five patients with diabetes mellitus, who at some time in the course of this disease presented the unusual combination of a low carbon dioxide content of the plasma with a negative ferric chloride in the urine. As an explanation of an absent ferric chloride reaction in the urine in threatened diabetic coma, in advanced diabetic coma under treatment, in diabetic coma with considerably increased blood ketones, the authors suggest that it is probably due to temporary renal impairment usually on a basis of dehydration.

Surgery, diabetes and insulin. Chabanier (H.), Lebert, Lumière & Lobo-Onell, *Presse méd. (Par.)*, 1927, **35**, 210; *Abst. J. Am. M. Ass.*, **88**, 1524.

The authors use insulin in prevention and treatment of acetonemia in surgical patients with diabetes. In external lesions with diabetes, it may be advantageously employed in general and in local treatment. It can be applied in the form of an ointment or a powder. The ointment is composed of 30 cc. of insulin, 1.5 gm. of zinc oxide, 45 gm. of wool fat and 90 gm. of petrolatum. Compresses with the ointment are renewed daily. If insulin powder is used, a compress with petrolatum is applied above the powdered area. Surprisingly good results were obtained in diabetic patients with operative wounds, trophic ulcerations of nervous origin, varicose ulcers, gangrenes, also with anthrax and furunculosis.

Influence of insulin on liver and muscle glycogen in the rat under varying nutritional conditions. Barbour (A. D.), Chaikoff (I. L.), Macleod (J. J. R.) & Orr (M. D.), *Am. J. Physiol. (Balt.)*, 1927, **80**, 243-272.

White rats, weighing between 110 and 150 grams, were used in the experiment. It was found that after 24 hours' starvation the blood sugar averaged 0.106%, the liver glycogen 0.16%, and muscle glycogen 0.30%. After 48 hours' starvation the values were: blood sugar, 0.103%; liver glycogen, 0.32%, and muscle glycogen 0.25%. The results on individual rats in each group varied within a narrow range of the average (probable error not above 0.05), except in the case of the liver glycogen after 48 hours' starvation, in which case the probable error was 0.110. The increase in liver glycogen after 48 hours is considered to be due to the accentuation of a process of glyconeogenesis setting in after the original stores of glycogen in the liver have been exhausted. Injection of sub-convulsive doses of insulin in rats from whom food has been withheld for 48 hours, invariably caused a decrease in percentage of glycogen in the liver, in the first hour after injection. After the injection of 1 unit per kgm., this returned to the normal in about 1½ hours, and rose decidedly above it in 2 hours, the glycogen of the muscles at both of these periods being definitely decreased. After somewhat larger but still sub-convulsive doses of insulin (2 to 3 units per kgm.) the decrease in liver glycogen became more pronounced and the return to the normal level retarded, although recovery became quite evident before there was any demonstrable increase in blood sugar. There was a pronounced decrease in the muscle glycogen after these somewhat larger doses. No evidence of hypoglycemic symptoms appeared in any of these animals. After feeding previously fasted animals on a standard diet containing abundance of starches, the following changes were observed: the blood sugar curve rose steadily until it gained a level of between 0.15 and 0.16%, which was

reached in about an hour after feeding, and maintained for between 5 and 6 hours; the glycogen in the liver steadily rose from the starvation level until after 6 hours four per cent was present; the muscle glycogen during the same period rose to about 0.40%. When moderate amounts of insulin were injected one hour after feeding the deposition of glycogen in the liver was definitely retarded at all periods up to 3 hours after the injection of insulin. The glycogen of the muscles in these animals did not meanwhile deviate beyond the experimental error involved in the observation in the uninjected controls. In later periods, namely, 3 to 5 hours after injection, the muscle glycogen might or might not be somewhat higher. When very large doses of insulin were injected into fed rats the inhibitory effect on glycogen formation in the liver became more marked and the percentage in the muscles became definitely greater than in the controls, the total gained by the muscles being of about the same magnitude as the total deficit in the liver. It is concluded that after active absorption of carbohydrate has been proceeding for some time large doses of insulin cause more glycogen to be deposited in the muscles, this being accompanied by an approximately corresponding decrease in the amount deposited in the liver. Under the same conditions smaller doses of insulin, while having the same effect on the glycogen of the liver as larger ones, cause no demonstrable change in the glycogen of the muscles. In fasted animals insulin always causes a decrease in the glycogen content of both liver and muscles, but before there is any demonstrable recovery in blood sugar the glycogen of the liver returns to or about the initial level.—Authors' Summary.

Blood calcium as affected by insulin. Brougher (J. C.), *Am. J. Physiol.* (Balt.), 1927, 80, 411-415.

In both normal and parathyroidectomized dogs the blood calcium is increased for a period of two and one-half hours following the administration of insulin.—Author's Summary.

On the metabolism of dihydroxyacetone in pancreatic diabetes. Campbell (W. C.) & Markowitz (J.), *Am. J. Physiol.* (Balt.), 1927, 80, 561-575.

Experiments with the triose, dihydroxyacetone, on depancreatized animals have shown that it is not metabolized in the absence of insulin but forms glucose and is excreted quantitatively as such. It raises the blood sugar of these animals and its conversion to glucose requires no insulin. Though its respiratory quotient is unity it does not raise that of the depancreatized dog when administered in adequate amounts without insulin. It is not antiketogenic in these animals. There is no evidence that it is an intermediary compound in the catabolism of glucose.—Authors' Abstract.

"Synthalin." De Jong (D.), *Nederl. Tijdschr. v. Geneesk.* (Amst.), 1927, **71**, 541; *Abst. J. Am. M. Ass.*, **88**, 1366.

Frank, Nothmann and Wagner have recently described a synthetic substitute for insulin. Studying the blood sugar effect of aminobuthylenguanidin, aminopenthyllenguanidine and aminoheylenguanidine, they found that lengthening the methylene chain in the molecules of guanidine compounds increased the hypoglycemic effect of the substances and decreased the toxic effect. In this way they prepared a compound with somewhat slower but more lasting action than insulin, which they call "synthalin." De Jong studied the properties of the preparation on two diabetic patients, aged 70 and 61. Peroral administration of "synthalin" decreased the glycosuria, in proportion to the amount administered; the decrease was 0.40 and 0.55 gm. of dextrose, respectively, per mgm. of "synthalin." The blood sugar showed also a regular decrease. The preparation had a cumulative effect which lasted for 24 hours, and which was first noticeable in a few hours after the administration. It cannot, therefore, be used in diabetic coma, where a rapid decrease of the blood sugar is desired. It is especially useful in treatment of patients with a high insulin resistance. The great advantage of "synthalin" is that it can be administered perorally.

Tolerance to different foods in diabetes. Depisch (F.), *Wien. Archiv. f. innere Med.* (Berl.), 1927, **13**, 653; *Abst. J. Am. M. Ass.*, **88**, 1528.

The author tested six diabetic patients for their tolerance to proteins, cereals and mixed diets. Cereals alone were tolerated better than a mixed diet. A little over one-half of the patients had a higher tolerance for a protein diet than for a mixed diet. The retention of food reserves is one of the sources of error. He believes that over longer periods the tolerance calculated according to the dextrose value of the food might be the same.

The effects of lowered body temperature and of insulin on the respiratory quotients of dogs. Finney (W. H.), Dworkin (S.) & Cassidy (G. J.), *Am. J. Physiol.* (Balt.), 1927, **80**, 301-310.

There is a fall in the respiratory quotient of a dog immediately after the administration of amytal. The respiratory quotient returns to its original value in from 30 to 60 minutes. The metabolic rate is greatly reduced by amytal anesthesia. Lowering the body temperature of a dog is in itself sufficient to cause the respiratory quotient to fall to a level as low as 0.032, provided that shivering has been suppressed. Even while the animal is shivering, the respiratory quotient may fall to a level far below 0.70. Therefore, lowering the body temperature of an animal causes a change in the character of its metabolism. The occurrence of shivering is asso-

ciated with a rise in the respiratory quotient indicating increased utilization of carbohydrate. The abolition of shivering, whether by means of insulin, curare, lowered body temperature, or anesthesia, causes the respiratory quotient of a dog to fall. The administration of insulin to a cooled dog that is not shivering causes the respiratory quotient to rise.—Authors' Summary.

Glycosuria after insulin (Glykosurie durch Insulin). Fricke (G.), *Klin. Wehnschr. (Berl.)*, 1926, 5, 1927-1928; *Abst. Physiol. Absts.* 12, 43.

Dogs were given 60 to 100 gms. cane sugar, and at the same time 20 to 35 units of insulin. The hourly excretion of reducing substances in the urine was followed, and it was shown that, compared with control experiments in which no insulin was given, a definite glycosuria was caused by the insulin. The insulin caused the usual fall in blood sugar. In an experiment on himself, in which 350 gms. cane sugar and 140 units of insulin were taken, the author found only a small increase of reducing substances in the urine. The author suggests that the glycosuria of pregnancy and renal diabetes may be due to a hyperfunction of the pancreas.

Maximum hypoglucemia without the use of Insulin. II. Geiger (E.) & Szirtes (L.), *Arch. f. exper. Path. u. Pharmacol. (Leipz.)*, 1926, 119, 1-23; *Abst. Chem. Absts.*, 21, 1494-1495.

Rabbits with the splanchnic sectioned may be sensitized by a diet of hay and beets so that the administration of atrophine or coli toxin causes a reduction in blood sugar. Apparently this diet causes a profound inhibition of the glyconeogenesis. The symptoms of the hypoglucemia can readily be abolished by injections of adrenaline or sugar. They occur only in animals with a sectioned splanchnic since in normal animals the adrenals exert a regulatory function. The effects of atropine on the concentration of blood sugar involves two factors; in normal animals it causes a hyperglucemia through a central stimulation; in the animal with the splanchnic sectioned it causes a hypoglucemia through inhibition of glyconeogenesis. The symptoms associated with the latter correspond almost exactly to those observed following the injection of insulin. The ensuing convulsions are not due to the hypoglucemia as such, but are referable to disturbances in carbohydrate metabolism. Hypothermia results from the carbohydrate impoverishment, and the latter, in turn, deranges the protein metabolism, this augmenting nitrogen excretion.

Xanthoma diabeticorum: Unusual process of involution. Goldstein (E.) & Harris (J.), *Am. J. M. Sc. (Phila.)*, 1927, 173, 195; *Abst. J. Am. M. Ass.*, 88, 1597.

A case of xanthoma diabeticorum is described, showing a pecu-

liar process of involution not previously mentioned in the literature. This occurred in a patient suffering from diabetes mellitus, to whom insulin was administered in the late stages of the disease. Three types of resolution went on simultaneously with little or no reference to the general condition: (a) The lesions on the palms disappeared completely; (b) those on the elbows coalesced and left large pigmented patches; (c) those on the legs and thigh underwent degenerative changes resulting in extensive scar formation—a process hitherto undescribed.

The effect of injected glucose on tolerance. Jordan (E. M.), *Am. J. Physiol. (Balt)*, 1927, **80**, 441-449.

Experimental evidence is given to support the hypothesis that incoming glucose acts as a stimulus to the islands of Langerhans, provoking a mobilization of insulin and thereby increasing the sugar-using power (tolerance) of the organism. As a corollary it has been demonstrated that when the tissues have obtained an optimal supply of insulin, additional insulin given by injection is inert.

—Author's summary.

Endocrine pancreas function after ligature of ducts (*Über das Verhalten der endokrinen Pankreasfunktion nach Unterbindung des Ausführungsganges*). Jorns, *Klin. Wchnschr. (Berl.)*, 1926, **5**, 2434-2437; *Abst. Physiol. Absts.* **12**, 108.

The observations of Mansfield on the increased sugar tolerance in dogs which results from ligature of the pancreatic ducts are confirmed. The author finds that the increased tolerance is first observed about two months after the operation, and lasts for about ten months. In rabbits the same phenomenon occurs, but only if the ligatured duct becomes patent again.

Insulin, arterial tension and glucemia. Jung (L.) & Auger (L.), *Compt. rend. Soc. de biol. (Par.)*, 1927, **96**, 287-289; *Abst. Chem. Absts.*, **21**, 1493.

Experiments with dogs showed that under ordinary conditions there is not necessarily any coincidence between the hypoglucemic and hypotensive actions of insulin; it has a hypotensive action independent of the diminution of the sugar in the blood.

Some influences of pancreatic hormone on the lymph. Katsura (S.) & Kozuka (K.), *Tohoku J. Exp. Med.*, 1926, **8**, 91-106; *Abst. Physiol. Absts.*, **12**, 108.

Insulin injected subcutaneously into rabbits in which the lymph is collected into cannulae from the thoracic duct and right lymphatic duct (thus not entering to the blood) causes a hypoglycaemia as low as 0.02% without any convulsions. If the lymph collected be

injected intravenously it does not cause convulsions, but a hyperglycaemia. Normal thoracic lymph injected intravenously causes hypoglycaemia. Insulin decreases the thoracic lymph sugar, while it increases the fat and lipoids. Adrenalin decreases the fat and lipoids of the thoracic lymph. In the normal starved animal the thoracic lymph fat and lipoids fluctuate somewhat, varying inversely as the variations in the blood and lymph sugar.

Action of Marienbad mineral water on the respiratory quotient and the metabolism of phosphorus in the diabetic. Kauffman-Cosla (O.) & Zorkendorfer (W.), *Compt. rend. Soc. de biol. (Par.)*, 1927, **96**, 281-282; *Abst. Chem. Absts.*, **21**, 1493.

By the administration of mineral water to the diabetic the respiratory quotient is raised by an increase in the elimination of carbon dioxide. This is paralleled by a diminution in the abnormal carbon constituents in the urine. At the same time there is a pronounced diminution of the elimination of urinary phosphorus.

Rapid disappearance from the blood of insulin injected intravenously. Kepinow (L.) & Lebert (S.), *Compt. rend. Soc. de biol. (Par.)*, 1927, **96**, 371-374; *Abst. Chem. Absts.*, **21**, 1493.

Dog A received an injection of insulin and in 3 minutes its blood was transfused to Dog B, previously bled. The sugar in the blood of A 1 to 3 hours after the transfusion was about one-half that in B. In a second experiment in which the transfusion was made in 30 seconds after the injection of insulin, the sugar in the blood of A for the 3 hours after the injection was markedly lower than in the blood of B. It is suggested that the insulin is fixed in tissues rich in glycogen.

The antiketogenic influence of insulin in diabetes mellitus. Killian (J. A.), *J. Lab. & Clin. M. (St. Louis)*, 1926, **11**, 1132-1139; *Abst. physiol. Absts.*, **12**, 43.

Observations on 7 cases of diabetes show that the administration of insulin causes an immediate decrease of the ketone bodies of blood and of urine, reaching a maximum in 4 to 6 hours. This decrease in ketosis is accompanied by a rise in the alkali reserve of the blood and a proportional increase in the blood pH. This influence of insulin is regarded as due to the more complete oxidation of the carbohydrates.

Insulin and diuresis. Klein (I.) & Rischawy (E.), *Ztschr. f. d. ges. exper. Med. (Berl.)*, 1926, **51**, 652-672; *Abst. Chem. Absts.*, **21**, 963.

There is a close relationship between the changes brought about by insulin in the H_2O metabolism of a diabetic and the action of this hormone on carbohydrate metabolism. The reduction in the amount

of urine, decrease in NaCl concentration in the urine, fall in NaCl content in the blood and concentration of the blood are indications of the extrarenal H₂O and NaCl retention brought about in the diabetic by insulin. The salt retention is connected with the increased binding of H₂O in the tissues caused perhaps by increased combustion of carbohydrates or increased deposition of glycogen or decreased breaking up of glycogen under the influence of insulin. The H₂O and NaCl retention are more marked when insulin is given without carbohydrates. Several hours after giving insulin there is a marked increase in H₂O and NaCl diuresis which is as yet unaccounted for, but may be due to stimulation of the vegetative nervous system. In a normal individual insulin causes only a transitory inhibition of diuresis, but there is no abrupt rise in diuresis after some hours as in a diabetic and there is no marked diuretic effect after both insulin and carbohydrates are given as in the diabetic.

Insulin in hepatic diseases. Klein (O.) & Holzer (H.), *Klin. Wchnschr.* (Berl.), 1927, 6, 157; *Abst. J. Am. M. Ass.*, 88, 1611.

Large doses of insulin (from 60 to 100 units daily) were administered to patients with diseases of the liver. The jaundice was influenced beneficially in almost all of them, including some with cirrhosis and cancer. The patients easily become hypoglycemic, even with a large carbohydrate intake.

Ability of the tissue cells to take up and fix sugar. Relation of tissue cells to the action of insulin and to diabetes. Kurokawa (T.), *Tohoku J. Exptl. Med.*, 1926, 8, 54-74; *Abst. Chem. Absts.*, 21, 954-955.

Absorption of sugar by body cells in the sense mentioned by Mendel, Engel and Goldscheider occurs in diabetic as in normal subjects. Such absorbed sugar is fixed only through healthy metabolism, and this fixation ability fails in the diabetic, in which the absorbed sugar again enters the circulation and finally appears in the urine. Insulin exercises no perceptible influence on the sugar-absorbing ability. On the other hand insulin promotes the sugar-fixation power whereby the organism is protected from an overflow of the blood sugar.

Increase in the insulin content of pancreatic venous blood after excitation of the vagus nerve. LaBarre (Jean), *Compt. rend. Soc. de biol. (Par.)*, 1927, 96, 193-196; *Abst. Chem. Absts.*, 21, 1484.

When the modified technic of Hedon was used, it was concluded that with 2 dogs in pancreatico-jugular anastomosis, if the peripheric end of the right vagus of the donor be electrically stimulated, the transfusion of pancreatic venous blood of this animal leads, in its congener, to a state of marked hypoglycemia.

It appears that the secretion of insulin in the venous blood of the pancreas increases under the influence of nerve modifications of vagal origin.

Existence of a physiologic insulinemia. LaBarre (Jean), *Compt. rend. Soc. de biol. (Par.)*, 1927, 96, 196-198; *Abst. Chem. Absts.*, 21, 1484.

By the transfusion of a relatively small quantity of pancreatic venous blood, the hyperglucemia in a dog previously depancreatized is reduced. The experiments also show that the blood issuing from the gland with its higher content of insulin has an anti-diabetic action much more marked than blood from the normal carotid. The existence of a physiologic insulinemia is accordingly considered as proved.

The action of insulin in glycogen formation and its therapeutic application. Lawrence (R. D.), *Quart. J. Med. (Oxford)*, 1926, 20, 69-86; *Abst. Physiol. Absts.* 12, 43.

Exercise lowers normal blood sugar slightly, but a diabetic blood sugar more markedly, and increases the action of insulin; but if a patient is accustomed to insulin, exercise without it increases the blood sugar, owing to glycogenolysis of the store formed under the action of insulin; but at the same time the arterio-venous difference is increased, showing that the muscles are utilizing glucose. In exercise with insulin much more of the glycogen store is utilized, resulting in late hypoglycemic symptoms. The insulin effect is more marked when the glycogen store is depleted, as in emaciated diabetic first coming under treatment; as the condition improves, more insulin will be required, but this does not imply a depreciation of the patient's condition. In a theoretical consideration of the action of insulin, the author concludes that its effect is anabolic, i.e., it acts by forming glycogen from glucose; its effect by increasing the carbohydrate metabolism in a diabetic is indirect, the increased metabolism following the increased amount of glycogen in the stores. The author considers that sugar can be formed from fat as well as protein; the former conversion is especially active when the glycogen stores are low, and ketosis then occurs, the ketone bodies being stages in the normal conversion of fat to carbohydrate. Insulin by supplying glycogen, the combustible carbohydrate, reduces the excessive conversion of fat (and protein) to carbohydrate and thus abolishes the ketosis. In treating a diabetic it is better for his comfort to have a carbohydrate store, even though this means a fluctuating blood sugar level and less chance of recovery of function by the islets of Langerhans.

Action of insulin on naphthalinic cataract. Michaïl (D.) & Vancea (P.), *Compt. rend. Soc. de biol. (Par.)*, 1927, **96**, 65; *Abst. J. Am. M. Ass.* **88**, 1524.

Rabbits were given naphthalene by mouth daily. As soon as lesions appeared in the lens, insulin was administered. Naphthalene was continued. Insulin appeared to retard markedly the occurrence of cataract. In another series of animals, insulin treatment preceded and accompanied the administration of naphthalene. Insulin was found to increase the resistance of the animal's organism to acute naphthalene poisoning. In a third series of experiments, naphthalene was given until lesions started in the lens, whereupon it was replaced by insulin. This resulted in disappearance of the lesion in the lens. The cure was transient in some animals, durable in others. The clinical course of some senile cataracts and the course of cholesterolemia in these cases suggest an analogy with naphthalinic cataract. The authors believe that at least some senile cataracts may be of pancreatic origin.

Effect of insulin upon the carbon dioxide content in the arterial blood sugar level in rabbits poisoned by carbon monoxide. Mikami (S.), *Tohoku, J. Exptl. Med.*, 1927, **8**, 378-383; *Abst. Chem. Absts.* **21**, 1494.

Insulin is capable of inhibiting the reduction of carbon dioxide content as well as hyperglucemia due to carbon monoxide poisoning. When it is applied to normal, non-poisoned rabbits, the carbon dioxide content in the arterial blood shows an inclination to reduce slightly.

The glycogen content of frog's muscle after injection of insulin and its relation to contraction. Olmstead (J. M. D.) & Harvey (J. M.), *Am. J. Physiol. (Balt.)*, 1927, **80**, 643-648.

The muscles of frogs can be rendered practically free from glycogen by causing them to have prolonged and violent insulin convulsions, i.e., the glycogen content is less than 0.2 mgm. per gram of muscle, the limit of detectability by the method of analysis used (Plüger's). Yet under these conditions the muscle is able to contract for hours upon being stimulated in the intact animal with maximal shocks from an inductorium, the height of contractions being virtually the same as in the normal frog's muscle stimulated for the same length of time.—Authors' Abstract.

Danger of insulin hypoglycemia in children. Priesel (R.) & Wagner (R.), *Klin. Wchnschr. (Berl.)*, 1927, **6**, 65; *Abst. J. Am. M. Ass.* **88**, 1362.

The authors believe that death from hypoglycemia in a diabetic child might be prevented if a large dose of dextrose were

injected immediately on the appearance of threatening symptoms; for instance, at least a 20 cc. of a 33% solution, intravenously. If considerable improvement does not take place instantaneously, they inject from 100 to 200 cc. of a 10% solution beneath the skin. When the patient regains consciousness, he should be given fruit or bread.

The presence of insulin-like substances in malignant tumors (*La existencia de insulinoideas en los tumores malignos*). Roffo (A. H.) & Correa (L. M.), *Bol. inst. de med. exp. de Buenos Aires*, 1926, **2**, 969-972; *Abst. Physiol. Absts.* **12**, 108.

A sarcoma of the rat has yielded from 500 grams of material 8 to 12 units of a substance with similar properties to those of insulin.

Glycemia and diseases of the stomach. Rosenberg (M.) & Kallner (A.), *Deutsche med. Wchnschr. (Berl. & Leipz.)*, 1927, **53**, 183; *Abst. J. Am. M. Ass.* **88**, 1611.

Gastric ulcer or nervous irritability of the stomach was found only rarely in diabetes (in about 1% of the patients). About one-quarter of the patients with innocuous glycosuria had these disturbances. Lability of the vegetative nervous system might be the cause of both phenomena in the latter group.

Diabetes mellitus and hypoglycaemia. Rosendahl (G.), *Acta Medica Scandinavica (Stockholm)*, 1927, **66**, 100-108.

A case of diabetes mellitus is reported in which repeated attacks of hypoglycemia were observed. The first attack occurred suddenly after treatment with insulin, but the last attacks occurred in spite of rather high carbohydrate diets and no insulin. Only glucose injections alleviated the symptoms. Although slight alkalosis was observed, an acetoneuria, high NH_3 , and excess of chloride and nitrogen were present in the urine. The patient died in hypoglycemia. At autopsy a completely sclerotic pancreas and a slight liver cirrhosis were found. Rosendahl suggests a liver insufficiency as the cause of hypoglycemia in such cases.

—M. O. Lee.

The influence of insulin on the acetaldehyde formation in the body of animals. Supniewski (J. V.), *J. Biol. Chem. (N. Y.)*, 1926, **70**, 13; *Abst. Physiol. Absts.* **12**, 46.

Acetaldehyde was determined in the blood and organs of several animals, including the rabbit, cat, and dog, by the method of Bougault and Gros. Insulin was found to increase the aldehyde content of the organs both in vivo and in vitro. The blood of depancreatized dogs contained 0.2 to 0.4 mgm. of total aldehyde

per 100 gm. of blood, the normal figure being less than 0.1. Insulin administration was found to abolish this excess. Administration of alcohol or aldehyde increased the amount of aldehyde in the blood. Insulin accelerated the subsequent return to normal.

Endocrine factors in oxalic acid metabolism. Viale (G.), *Rev. sud-americana endocrinol. immunol. quimioterap.*, 1926, **9**, 967-977; *Abst. Chem. Absts.* **21**, 954.

Insulin injections do not alter the $C_2H_2O_4$ content of the blood of rabbits and dogs, but cause a marked decrease of its excretion in urine. The latter is also observed in diabetes. A considerable increase of oxalaturia appears as a result of adrenaline injections and of pancreatectomy. Daily adrenaline injections have an increasing influence on glucosuria. Phlorhizin diabetes has no noteworthy effect on $C_2H_2O_4$ excretion. Oxalic acid is an intermediate of sugar metabolism. Its production is controlled by the internal secretion of the pancreas. Insulin is indicated in oxalatemia.

Rôle of carbohydrate retention in hypertension. Weiler (E. S.), *Semana méd. (Bs. Aires)*, 1927, **34**, 155; *Abst. J. Am. M. Ass.* **88**, 1525.

The author reviews his work on the rôle of carbohydrate retention in the etiology of arterial hypertension. According to his theory, hypertension, as well as obesity and diabetes, is a manifestation of insulin deficiency. Long before Wohl, Weiler had referred to the need of vitamins in diets prescribed for diabetic patients.

Increase in the insulin content of the pancreatic venous blood after hyperglucemia caused by the injection of glucose. Zunz (E.) & LaBarre (Jean), *Compt. rend. Soc. de biol. (Par.)*, 1927, **96**, 421-423; *Abst. Chem. Absts.* **21**, 1489.

By the pancreatic-jugular anastomosis a transfusion experiment was made with dogs, which proved that the insulin content of the pancreatic vein is increased after an intravenous injection of a large dose of glucose.

Osteitis fibrosa. Mandl (F.), *Arch. f. klin. Chir. (Berl.)*, 1926, **143**, 245; *Abst. J. Am. M. Ass.* **88**, 1610.

The relations between the parathyroids and diseases of the bone are discussed. Forty-four cases were collected from the literature in which enlargement of the parathyroids was associated with rickets, osteitis deformans, osteomalacia, senile osteoporosis or generalized osteitis fibrosa. The author describes a case in which he removed a parathyroid tumor on therapeutic grounds in a severe case of generalized osteitis fibrosa. The excretion of cal-

cium in the urine had decreased five-sixths a few days after the operation. The general condition underwent remarkable improvement, the pains became slight and came on only at times of changes in the weather. Motion has entirely returned in the joints of the extremities and the patient, who before the operation could neither stand nor walk, can now stand without difficulty and walks with a cane and a crutch. This case seems to destroy the validity of Erdheim's theory of compensatory hypertrophy on the part of the parathyroids. Animal experimentation aiming to produce pictures similar to osteitis fibrosa by trauma and washing out the marrow were negative. The pictures were obtained when coagulation of the blood was retarded by injections of citrate.

Hydrogen ion concentration and carbon dioxide content of blood of parathyroidectomized dogs. Wenner (W. F.) & Muntwyler (E.). *Proc. Soc. Exper. Biol. & Med. (N. Y.)*, 1927, **24**, 480-482.

A condition of alkalosis does not exist either before or during tetany following parathyroidectomy. The conclusions are based on measurements of pH and carbon dioxide content of plasma and calcium content of serum in three dogs.—J. C. D.

Influence of experimental hypothyroidism upon gastric secretion. Chang (H. C.) & Sloan (J. H.), *Am. J. Physiol. (Balt.)*, 1927, **80**, 732-734.

Thyroidectomy in two dogs caused an increase in the volume and acidity of gastric juice. Thyroid feeding before thyroidectomy caused a decrease of gastric secretion, both in amount and acidity. Thyroid feeding after thyroidectomy also depressed gastric secretion. The depression disappeared when thyroid feeding was stopped.—M. O. Lee.

Water metabolism in myxedema and exophthalmic goiter. Falta (W.) & Höglér (F.), *Wien. Archiv. f. innere Med. (Berl.)*, 1927, **13**, 547; *Abst. J. Am. M. Ass.* **88**, 1528.

The authors found sodium strongly hydropigenic and potassium and calcium antihydropigenic in myxedema. The water test diuresis was above normal. Preliminary administration of salty food increased the water and salt-water diuresis, while it inhibited it in normal individuals. In exophthalmic goiter patients, the opposite results were seen. They conclude that in these conditions the change is less one of the speed of salt transportation than one of the hydration condition of the colloids of the tissues.

Effect of potassium iodide and thyroid extract on thyroid gland of guinea-pig. Gray (S. H.), Haven (F. L.) & Loeb (Leo). *Proc. Soc. Exper. Biol. & Med. (N. Y.)*, 1927, **24**, 503-505.

If guinea pigs are fed potassium iodide, their thyroid glands

show an increased number of mytoses with no change in the size of the acini. After the treatment has been continued for more than six weeks the mitotic figures decreases in number, the epithelium becomes lower, and the acini enlarge and are filled with solid hard colloid. - In thyroid-fed guinea pigs, the epithelium is low, mitotic figures few, and the colloid hard. The author suggests that potassium iodide stimulates the gland to produce an excess of colloid. There being no call for this excess, it is eventually stored up in the gland in amounts sufficient to produce regressive changes. Thyroid feeding by supplying the body directly results in very rapid storage of colloid in the gland with similar regressive changes.—J. C. D.

On the innervation and secretory path of the thyroid gland. Hicks (C. S.), *J. Physiol. (Lond.)*, 1926, 62, 198-202; *Abst. Physiol. Absts.* 12, 49.

In normal dogs thyroglobulin passes out of the thyroid by veins and lymphatics. The rate of secretion is uninfluenced by stimulation of the sympathetic, but appears to be increased on administration of iodine.

The effect of the administration of cod liver oil upon thyroparathyroidectomized dogs. Jones (J. H.), *J. Biol. Chem. (N. Y.)*, 70, 647 (1927).

Daily ingestion by mouth of 20 cc. of cod liver oil for two weeks before thyroparathyroidectomy prevented tetany and greatly increased the length of life in dogs. If the oil is given only after operation there is no effect. The ingestion of the oil had little effect on the change in blood calcium. Similar results were obtained by irradiation of the animals.—J. B. Brown.

Thyroid disease: Diagnostic value of the Kottman reaction in thyroid dysfunctions. Katayama (I.), *Am. J. M. Sc. (Phila.)*, 1926, 172, 84; *Abst. J. Lab. & Clin. M.* 12, 713.

The basal metabolic rate is to be the most dependable laboratory index of thyroid activity. Increased thyroid secretion produces a lowering of the tolerance for carbohydrate, but there are numerous other conditions in which the tolerance for carbohydrate may be diminished. Hence the occurrence of high blood and urine sugar curve after the ingestion of glucose is not in itself indicative of hyperthyroidism. In hyperthyroidism, however, the blood and urine sugar curves after glucose furnish information concerning a phase of carbohydrate metabolism which is not gauged by the basal metabolic rate. The basis of the Kottman reaction is obscure, and hence it is difficult to say in what manner thyroid activity influences it. Such a reaction can only be accepted with skepticism. From the data reported in this paper it is evident that the results of the Kottmann reaction are not in accord with the

basal metabolism or the glucose tolerance. The retardation of the reduction of the silver iodode to silver occurs in many and various conditions patently not due to hyperthyroidism. Its diagnostic value in detecting hyperfunction or hypofunction of the thyroid is very dubious. It cannot be accepted as a substitute for the determination of the basal metabolic rate of glucose tolerance.

Synthetic thyroxin—clinical tests. Lyon (D. M.) & Redbead (F. A.), Edinb., M. J., 1927, **34**, 194-199.

Report of two cases treated with thyroxin produced according to the method of Harington and Barger. These cases showed an increase in basal metabolism of 1.85% to 3.43% per mgm. of drug and the physiological improvements to be expected from the administration of thyroxin.—J. C. D.

Ante-mortem protein decomposition after thyroidectomy (Beiträge zur Physiologie der Schilddrüse. X. Prämortaler Eiweisszerfall bei Schilddrüsenlosen Hunden). Mansfeld (G.) & Lanczos (A.), Biochem. Ztschr. (Berl.), 1926, **179**, 186-193; Abst. Physiol. Absts. **12**, 114.

In thyroidectomized dogs dying from starvation within a month of the extirpation, increased protein decomposition could not be detected in 3 out of 4 cases.

The effect of large doses of iodine on heat production in rabbits. Marine (D.), Deutch (M.) & Cipra (Anna). Proc. Soc. Exper. Biol. & Med. (N. Y.), 1927, **24**, 657-662.

Eighteen rabbits were treated with Lugol's solution or with potassium iodide and tested to see if they showed a change in heat production. Eleven showed no change, two a rise, and five a decrease. No relation between the response to treatment and the histological condition of the thyroid gland could be observed.

—J. C. D.

Effect of ergotamine tartrate on the heat production of normal and thyroidectomized rabbits. Marine (D.), Deutch (M.) & Cipra (Anna). Proc. Soc. Exper. Biol. & Med. (N. Y.), 1927, **24**, 662-664.

Ergotamine tartrate, a drug whose action neutralizes the action of adrenin, reduces the heat production of normal rabbits markedly and of thyroidectomized rabbits slightly.—J. C. D.

Relation of hypothyroidism to obstetrics and gynecology. O'Keefe (C. D.), South. M. J. (Birmingham), 1927, **20**, 375-379.

Hypothyroidism, in and around St. Louis, is a common disease among women. The patients present characteristic histories, physi-

cal findings, and metabolic changes, which make the diagnosis comparatively easy. Infection, normal pregnancy, abortions, miscarriages, and operations play an important role in the etiology of thyroid deficiency, the hypothyroidism in turn having a marked influence on pregnancy and sexual life in general. Severe menopause changes are due to glandular deficiency in general, and to thyroid in particular, and are not due to ovarian death alone. Relief from these disturbing symptoms through thyroid medication, providing the offending cause has been removed, is obtained in a very large percentage of cases. The cure depends almost entirely upon the duration of the disease.—Author's Abstract.

Is thyroidectomy the primary cause of the arrested development of skeletal muscle in cretin sheep? Simpson (Ethel D.), Am. J. Physiol. (Balt.), 1927, **80**, 735-738.

The non-development of muscle fibers in young sheep after thyroidectomy is considered as being due to the reduced bodily activity, rather than to the athyroid conditions. Control sheep, lethargic after being stunted by parasitic worms, showed the same non-development of striated muscle.—M. O. Lee.

Endocrinology

The Bulletin of the *Association for the Study of* **Internal Secretions**

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SUPRARENAL CARCINOMA WITH PUBERTAS PRAECOX IN A BOY THREE YEARS OF AGE*

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Stanley, 3 years of age, was admitted to the Long Island College Hospital for precocious development, cough and dyspnea. He was the third child of normal parents who stated that there was no history of any similar sexual precocity in either the immediate or remote family.

A large infant weighing eleven pounds at birth, he developed normally until the ninth month, when it was noted that the external genitalia began to assume proportions abnormal for a child of his age. This increase in size continued until the second year, when there was an apparent cessation in growth of these parts. Pubic hair, which appeared at twelve months, rapidly increased in amount and extent, so that by the second

*From the Departments of Pediatrics and Pathology, Long Island College Hospital. Read at the Eleventh Annual Meeting of the Association for the Study of Internal Secretions, Washington, D. C., May 17, 1927.

year the suprapubic and perineal regions were involved. There was a simultaneous growth of hair on the face and back. Accompanying these physical alterations there were psychological disturbances evidenced by a change in disposition, refusal to play with his former playmates or with children of his own age, the assumption of a serious manner and worried look, and a tendency to sleep most of the time. His voice became gruff and soon assumed adult quality. At no time, however, did he show any priapism nor any evidence of nocturnal emissions or masturbation. Three weeks prior to admission dyspnea set in, followed later by cyanosis.

Upon admission to the hospital the following salient features were found on examination:

The general appearance gives one the impression of an adult dwarf with the musculature and general development of

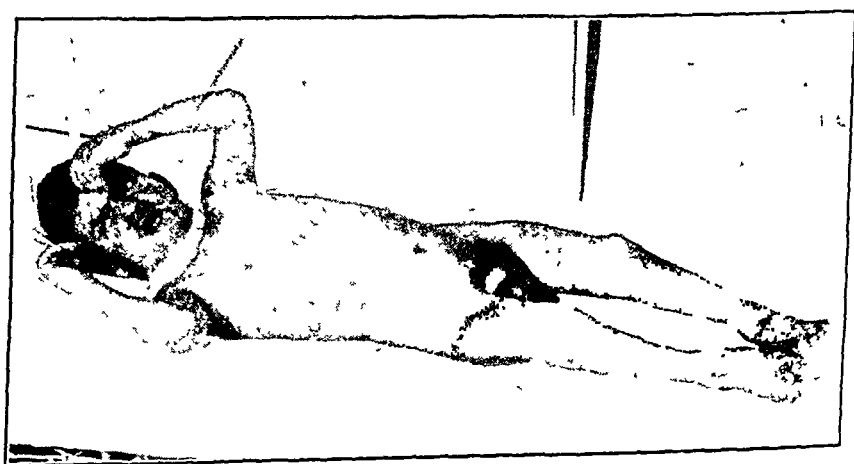


Fig. 1.—Photograph of patient on admission to hospital.

a young Hercules. The face is that of a boy of puberty with a well marked *acne vulgaris*. The thorax is well shaped and manly in its proportions. The extremities are short and stocky. The child is dull, however, responding slowly to questions in a gruff and low pitched voice. The skin is of good tone and turgor with no pigmentation.

The scalp is covered with thick hair extending well down over the forehead and posteriorly down on the neck. The eyebrows are heavy, shaggy and continuous across the bridge of

the nose, and the eyelashes are long and coarse. The face, upper lip, chin, back, pubic and perineal regions show marked growth of hair.

Eye fundus examination reveals retinal veins which are full and tortuous. Each disc is of normal color with clear outlines. The lips are cyanotic. Over the right supraclavicular region is a mass of glands in the center of which is a small incision with necrotic edges.

There is an equal excursion of both sides of the chest. The percussion note is impaired, shading from dullness to flatness over both sides. In various areas moist fine and medium rales may be heard, while in other areas the breathing is diminished in intensity.

The abdomen is flat and soft. The spleen is palpable two fingers breadth below the costal margin, and immediately below the spleen can be felt another mass which is firm, large and lobulated, extending from just above the umbilicus and occupying the entire flank. This mass is firmly fixed posteriorly and is tender on palpation. The percussion note is tympanitic except over the splenic area where it is flat. The liver is not palpable.

The penis and testicles are well developed, the penis being 7.8 cm. in length and 6.6 cm. in circumference. The scrotum is large. The right testicle is slightly larger than the left. The right epididymis is unusually large. On both sides the epididymi are easily palpable. On rectal examination can be felt a smooth, homogeneous, firm prostate.

Roentgenological examination of the chest, which includes the clavicles, shoulder joints and practically all of the left humerus, shows this portion of the skeleton markedly increased in size for a child of this age. All but one of the changes present should be normally found in a child of this size and aged about 7 to 10 years. The exception is in the length of the humeri, which is not longer than one would expect in a 3 to 4 year old child, although the bone itself is much heavier in structure than it should be in a child of this age. The development of the head of the humerus, of the tuberosities and of all other bone structures is proportionate in size to the skeleton normally seen in a 7 to 10 year old child.

The sella turcica is of a type A (18), that is, circular:

the anterior clinoid processes are short and heavy, the posterior clinoids very heavy and reasonably straight. The outline of the sella turcica itself is normal. There is no erosion and, while the size of the sella is diminished slightly, it is well within normal limits. That portion of the skull incidentally shown on the sella turcica film shows again characteristics of a child of 7 to 10 years of age. The mastoid ethmoid and antral cells show the development for the age of 7 to 10 years. The frontal cells and sphenoid are still very small, as they usually are in a child of this latter age. Dentition is within the normal limits for a child of 7 to 10 years, although apparently all of the primary incisors are present.

Both lungs are riddled with tumefactions. A plain film of the abdomen shows some enlargement of the liver and spleen and on the right there seems to be some enlargement of the right kidney. The lower pole of the right kidney appears smooth, while that of the left kidney is not definitely made out.—Dr. A. L. L. Bell.

LABORATORY DATA

The *Wassermann* and *von Pirquet* reactions were both negative. The blood count showed: red blood cells, 4,544,000; white blood cells, 19,600; hemoglobin, 100 percent; polymorphonuclear cells, 68 percent; large and small lymphocytes, 28 percent; mononuclear cells, 4 percent.

Urinalysis: Urine cloudy, amber in color, acid in reaction, specific gravity, 1020, negative to albumin, glucose, diacetic acid and acetone bodies. Numerous red blood cells found, 15 white blood cells to the field, no casts.

Course in hospital: The child remained from July 1, 1925 to July 5th on which day he died. During his stay in the hospital, the temperature ranged from 99 degrees on admission to 100 and 102. The respirations were about 32 to 35 and the pulse 100 to 106. The picture was that of a progressive pulmonary complication superimposed upon the metastatic consolidation of the lungs.

Measurements of the Body:

Length, 110 cm.

Circumference of head (maximum), occipito-frontal, 51 cm.

Pupillary distance, 5.6 cm.

Length of nose, 3.4 cm: external nares, maximum diameter, 1 cm.

Width of oral fissure, 7.5 cm.

Circumference of the neck, midportion, 28.2 cm.

Circumference of chest at nipple, 60.5 cm.

Episternal notch to upper portion of symphysis pubis, 39.6 cm.

Episternal notch to xiphoid process, 12.6 cm.

Circumference of abdomen at umbilicus, 54 cm.

Circumference of pelvis at level of anterior superior spine (at ilia), 54.4 cm.

Upper extremities—Circumference of left arm, midportion, 16.8 cm.

Right arm, midportion, 17.5 cm.; left forearm, midportion, 15.1 cm.

Right forearm, midportion, 16.5 cm.; left acromion process to styloid process, 30 cm; same for the right side.

Lower Extremities: Anterior superior spine to internal malleoli (both sides), 46.5 cm.

Circumference of left thigh, midportion, 26.2 cm.

Circumference of left calf, 18.3 cm.; of right calf, 18.7 cm.

Length of left foot, 16.8 cm.; of right foot, 16.4 cm.



Fig. 2.—Tumor occupying site of left suprarenal gland with extension into the left suprarenal vein, left renal vein and inferior vena cava. Cut surface of inferior vena cava seen near the right kidney. Right suprarenal gland not found.

AUTOPSY FINDINGS

(Mention is made of only the important findings.)

Skull. There is no evidence of any pathological condition within

the skull. The pituitary and pineal glands are both normal on appearance and on section.

Thorax. Both lungs are filled with numerous tumors ranging in size from that of a pea to that of a small lemon. The tumors near the surface are still covered with visceral pleura on the left side with the exception of one small tumor in the lingula pulmonis. The tumors are moderately firm and granular in consistency but

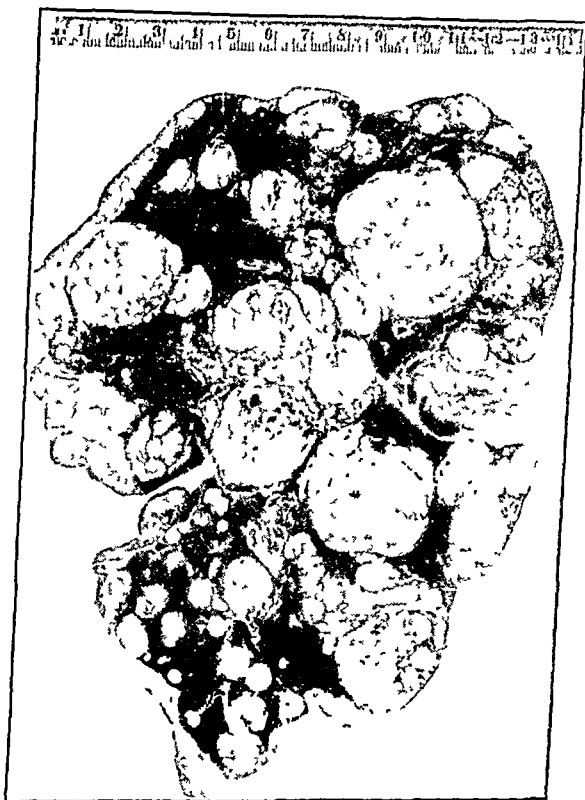


Fig 3—Metastatic growth in lungs.

none are extremely hard to the touch. On section they are found to be well circumscribed and very cellular; several present necrotic centers filled with a pink grumous material while others show a yellowish tint. The distribution of this yellow color is irregular, occurring in areas with scallop like borders surrounded by a tissue which simulates the appearance of that of normal brain.

The entire mediastinum with the perihilar regions is filled with large tumor masses, one very large mass extending from the root of the right lung upward to the region of the junction of the right clavicle with the sternum. This large tumor mass is soft and on section shows a greyish color throughout except for a small necrotic center filled with a putty-like material. The smaller tumors are

firmer and contain what appear to be two types of tissue—scattered areas of a yellowish tint surrounded by a softer, light grey, very cellular tissue. The thymus is normal in appearance, weighs 10 gms., and is 7 to 8 cm. in thickness. The thyroid gland is slightly enlarged and on section shows an increase in colloid contents. The parathyroids could not be located.

Abdomen. Occupying the left suprarenal region and extending from the dome of the left diaphragm downward to the upper pole of the right kidney and medially to the midline, there is present an irregular nodular surface tumor mass lying entirely retro-peritoneally. The mass is fairly movable. It has an increased blood supply as shown by the large suprarenal artery and vein. The suprarenal branch of the left renal vein is larger than the renal branch itself. The tumor extends into the lumen of the suprarenal vein medialward into the inferior vena cava almost occluding its lumen. The primary tumor shows on section a picture similar to that found in the metastases in the lungs and mediastinum except that the yellow tinted tissue is firmer and greater in amount.

Careful search of the right suprarenal area discloses at the upper pole of the kidney a rectangular structure which is infiltrated with fat to such an extent that it cannot be definitely determined whether or not it is adrenal tissue. After careful sectioning of the parts nothing but fat tissue was found. Neither the right suprarenal gland nor the right suprarenal vein could be found.

The pancreas and spleen are normal. The prostate gland is moderately enlarged and on cut surface shows a homogenous consistency. The seminal vesicles are filled with a thin glairy fluid. The right epididymis is larger than the left but does not present any abnormal findings.

MICROSCOPIC EXAMINATION

(Dr. M. A. Goldzieher)

The primary tumor consists principally of necrotic tissue but some alveolar structure is still discernible, showing large alveoli walled off by capillaries or wide thin-walled sinuses. The densely packed tumor cells vary in size and present two types, a small cell with a well-stained granular cytoplasm and a much larger one, highly vacuolized, with only minute remainders of cytoplasm. The nuclei are small, round, fairly regular and rather hyperchromatic.

In the metastatic nodules, particularly in those of the lung, the structure of the tumor resembles much more that of the adrenal cortex. The close relationship of the trabecules formed of the tumor parenchyma and the thin walled capillaries is particularly noteworthy. The tumor parenchyma is polymorphous, showing areas of very large cells with giant and hyperchromatic nuclei prevailing and others of very small densely packed cells. In some places both types intermingle.

That portion of the adrenal gland not affected by the tumor is normal on gross examination. Microscopically, however, the cortex seems to be hyperplastic. The glomerular layer is pronounced, the glomeruli being composed of unusually large and foamy cells. The trabecular layer is particularly abundant, its cells containing large deposits of lipoid. The reticular zone is small and intensely pigmented. The medulla is well developed and consists of fairly large cells with basophilic cytoplasm and also of cell groups of a much smaller type. The latter have scant cytoplasm but the alveolar structure of these cell groups proves that they are not lymphocytic.

The thyroid gland shows increased hyaline stroma. It is well vascularized and lobular of structure, the lobules containing irregular acini filled with a homogenous colloid and extensive desquama-

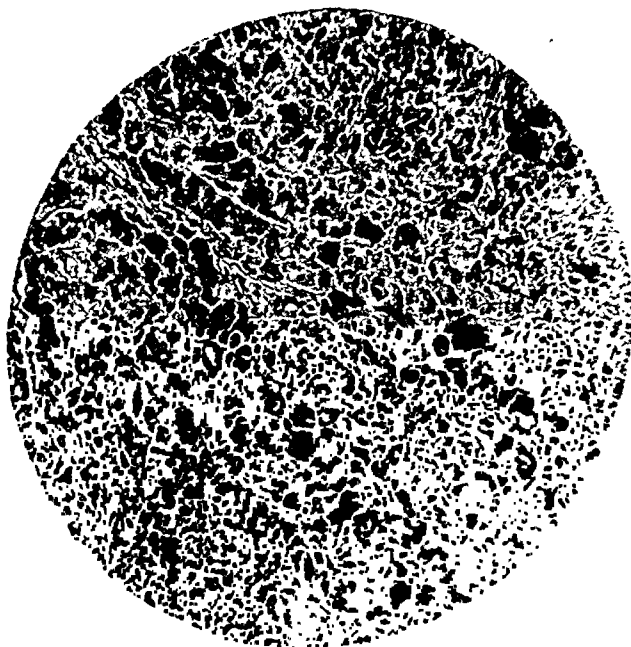


Fig. 4.—Primary adrenal tumor showing polymorphism of cell nuclei with some giant cells.

tion. Some areas show a more cellular parenchyma with small acini or none at all.

The pancreas does not show much pathological change. The islands are fairly numerous and some are unusually large.

The testicle is well developed. The interstitial cells are not very abundant. The seminal tubules are mostly solid and have no lumen as yet. Ripe spermatocytes cannot be seen.

The thymus gland is of lobular structure, its parenchyma lobules being separated by a rather fibrous connective tissue. The parenchyma proper is also infiltrated by connective tissue showing hyaline degeneration. Fat tissue is absent. The thymus parenchyma consists

of a dense mass of cells, the nuclei of which are like lymphocytes while scattered in between these are areas of larger less densely packed cells. There is an enormous number of concentric Hassel's corpuscles of various sizes and numerous vacuoles left by the vanished corpuscles. The entire appearance of the thymus is that of involution.

DISCUSSION

Pubertas praecox may be induced by hyperplasia or tumors of the pineal gland, adrenal cortex or the gonads. No case has been reported in which this condition was associated with dis-

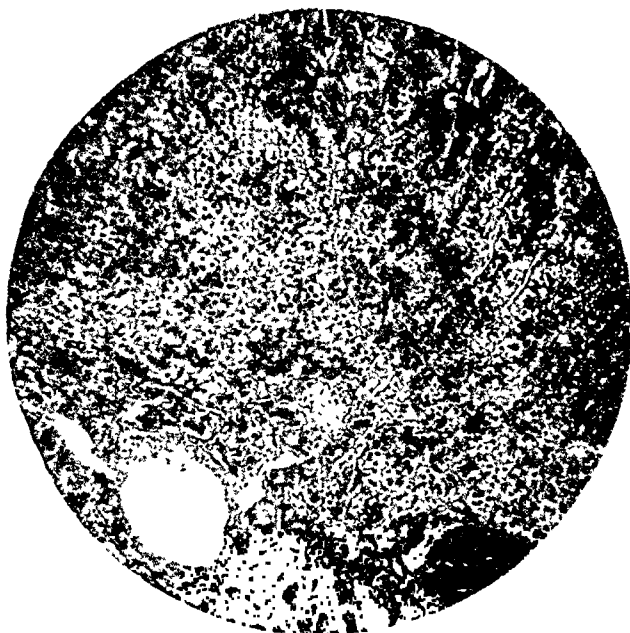


Fig. 5.—That part of adrenal cortex which was not involved by the tumor. Gives the impression of the adrenal of an adult showing all three layers of the cortex well developed. The involution changes in the reticularis which should be present in the adrenal gland of a three-year-old boy cannot be made out.

orders of the pituitary gland, thyroid or adrenal medulla.

Tumors of the suprarenal cortex or interrenal gland accompanying precocious sexual changes in children were first described by Linser in 1903 (1) and more fully in 1905 by Bulloch and Sequeira (2), who included a study of the cases previously reported in the literature. Since then this subject has been well reviewed by Glynn (3), Hoag (4) and Collett (5). Excluding the present one, there are in the literature 23 cases of pubertas praecox that have been confirmed by operation or autopsy; 19 of these are in girls and 4 in boys. Ours is the fifth case

to be reported in boys and the twenty-fourth in the literature. The other cases observed and reported in boys were by Linser (1) in one of five years and seven months who had left suprarenal hypernephroma which ruptured into the left vena cava and showed metastases in the lungs; by Adams (6) of a boy 14 years old with a left suprarenal perithelioma, in whom the symptoms began at the age of ten years; by Guthrie and Emery (7) in a boy of four years and four months who first showed symptoms at two years, and the fourth case by Tschernobrow (8) in an eleven-year-old boy. Collett (5) reported the only case in the lit-

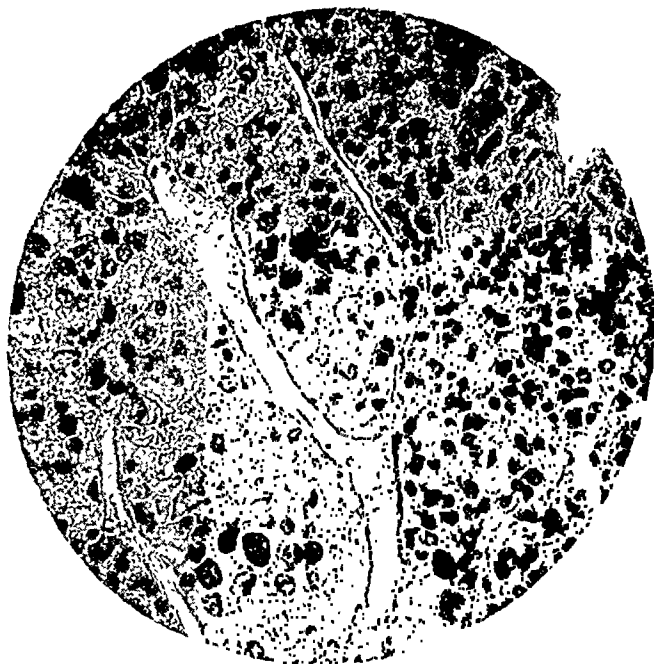


Fig. 6.—Section of tumor metastasis in lung showing trabecular structure and wide inter-trabecular sinuses. Part of the tumor tissue shows necrosis. Note the polymorphous element in cell nuclei of the tumor.

erature the subject of which survived operation. His patient was an eighteen-months-old girl who showed abnormal pubic hair growth at six months of age and at two years presented a picture of partial hermaphroditism, or, rather, feminine pseudo-hermaphroditism with hypertrophy of the clitoris and deep voice. Operation revealed a hypernephroma of the cortex which was removed. When examined two years following the operation, all abnormal hair growth had disappeared except some scanty dark hairs on the labia majora, and there was less fat.

but the voice did not show any change nor did the hypertrophy of the clitoris recede.

The sexual changes produced by disorders of the suprarenal cortex vary in their clinical picture according to the age at which the disease appears. Apert (9) originally described five classifications of adrenal cortex hyperplasia which were later modified into the following three groups (10) as a more adaptable working arrangement:

1. Interrenal hyperplasia occurring during fetal life producing pseudohermaphroditism. In this condition the internal sex glands are hypoplastic and the external sex organs are of the opposite sex to which the child really belongs. The true



Fig. 7.—Thymus showing involution changes consisting of formation of fibrous connective tissue. Exceedingly rich in Hassall's corpuscles, some of which have dropped out, leaving vacuoles.

sex of an individual depends upon the character of the internal sex glands.

2. Early post-natal interrenal hyperplasia producing a condition of pubertas praecox. The clinical picture here differs according to the sex of the patient. In the male there is an accentuation of the male characteristics, while in the female there is a tendency to a change towards the male type accompanied by secondary sex characteristics simulating the latter.

such as hypertrichosis, masculine voice, enlarged clitoris and absence of menstruation.

3. Interrenal hyperplasia occurring after puberty producing virilism or hirsutism affecting women between the ages of 15 and 25 years of age and showing sex characteristics tending toward the male type. Gallais in 1914 (11) collected 51 cases of adrenal cortex hyperplasia with genito-adrenal syndrome, all occurring in women and children.

The manner in which interrenal hyperplasia or cortical tumor produces this syndrome has been interpreted from various viewpoints and has given rise to several theories. Some are predicated upon the supposition that the physiological function of this gland is the promotion of body growth and the development of secondary sex changes (12). Tumors are considered as hyperplasia of the cortical tissue with a resulting cortical or interrenal hypersecretion. In support of this theory is mentioned the increase in size of the adrenals during pregnancy and the hyperplasia accompanying pubertas praecox and contrariwise the small cortex found in deficient sex development. Krabbe (31), however, contends that the tumor of the cortex develops from sex gland cells of masculine type which early in life of the embryo have been involved in suprarenal gland cortex and that an increase in these tumor cells produces the masculine features seen in the genito-adrenal syndrome. As a discussion of the relative worths of the various theories is outside of the scope of this report, those interested in this question are referred to the special articles on this subject. [Collett (5) discusses this at length].

The onset of puberty is accompanied by general systemic disturbances and alterations. From a developmental viewpoint a child of three years of age, herein reported, was really in the age of puberty as demonstrated by his excessive body and muscular growth; by hastened ossification, as depicted by the x-ray examination and, finally by the condition of some of his glands of internal secretion, which showed changes normal for puberty but abnormal for a child of three years.

The size of the suprarenal gland at birth is relatively enormous, the increase being especially marked in the cortex. During the first year of life the cortex undergoes a physiological involution in the form of gradual degenerative changes (14).

The zona reticularis tends to disappear completely and in its stead the medullary substance grows in proportion to the disappearance of the former, and eventually nothing but a vascular connective tissue zone forming a boundary between the medulla and cortex is left of the reticular zone. This can be seen even in a five year old child. As soon as this zone of connective tissue disappears, the medulla and cortex join, but with increasing age a new reticular zone is formed by the zona fasciculata and in adults reaches full growth. In our case the findings in the part of the adrenal cortex not affected by the tumor approximated those present in adult life rather than those generally found in a boy three years of age. In addition to this there was a developmental anomaly in that the right suprarenal gland and the right suprarenal vein were absent.

The thymus gland showed involution changes. According to Hammar (15) and others the thymus progressively increases in weight until the time of puberty when it undergoes involution with a gradual reduction in the parenchyma. Based on the results of his recent experiments, Jaffe (16) thinks that the suprarenals play some as yet undecided part in the involution of the thymus. The thymus and lymphoid tissue hyperplasia present during the period of infancy he believes to be manifestations of interrenal and gonad underdevelopment. He claims that the hyperplasia of the thymus which he found following suprarenal ablation in rats is due to a disturbance of relationship between the gonads, thymus and interrenal glands. The thymus involution in our case with an interrenal hyperplasia would tend to strengthen his contention of a thymo-interrenal relationship. Hammett (17), however, denies this relationship, claiming that the thymic involution of puberty is merely a reaction to the general physiological disturbance of the period.

The gonads in the present case show immaturity corresponding to the actual age of the child. There was no spermatogenesis. This is in keeping with the observations reported by others that in boys there is a premature development of the external sex organs but not potency. Sex power develops later and not as rapidly.

The pituitary gland and the pineal were normal on gross examination. Unfortunately the sections from both of these glands were lost before microscopic study could be made.

The pancreas and thyroid glands did not show any changes peculiar to puberty.

SUMMARY

The case is reported of a boy, three years of age, who presented symptoms of pubertas praecox, the onset being noticed at the age of nine months. He was of Herculean build, had a mannish voice, acne, pubic hair, light mustache, external genitalia of a boy of sixteen years, and premature ossification. His mentality was somewhat below that of a child of his actual age. Autopsy showed a carcinoma of the left suprarenal gland which extended into the left suprarenal vein and inferior vena cava and metastases in the lungs. The right suprarenal gland and right suprarenal vein were absent. That portion of the left suprarenal gland not involved by the tumor showed a picture generally found at the time of puberty; the thymus showed involution; the thyroid contained colloid; the pancreas, pituitary and pineal glands were normal. The testes were immature and did not show any spermatogenesis.

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THE RELATION OF CERTAIN GLANDS OF INTERNAL SECRETION TO THE DEVELOPMENT OF ATHEROSCLEROSIS*

SHEPARD SHAPIRO, M.D.

Hardening of the arteries has been repeatedly discussed in the literature for upward of three and a half centuries. It was noted by Amatus Lusitanus who made a study of the valves of blood vessels over seventy years before Willam Harvey brought forth his immortal work. More recently an immense amount of investigation has been done and a vast amount of literature has been published on the subject. However, although almost every conceivable phase of the problem has been studied, nevertheless there still remain to be demonstrated the underlying conditions which determine the development of atherosclerosis.

Because it is so well known I shall not present any detailed description of the histology of atherosclerosis. However, I would like to emphasize one stage in its development, namely, that in which the earliest detectable changes appear. It is upon this that the subsequent alterations depend. As far as the causation of the disease is concerned it can be stated that those conditions which lead to the formation of these primary structural disturbances are the conditions responsible for the development of atherosclerosis. These initial changes consist of a deposition of fatty substances (chiefly cholesterol and its esters) in the deep strata of the intima and consequent thickening of this layer. Large irregular shaped cells make their appearance and take up some of the fatty material. Aggregations of these (fatty deposits, layers of "foamy" cells, thickened intima) form the atheroma. The more advanced alterations soon follow. Separation and splitting of the elastic fibers occur, fibroblasts appear, and connective tissue overgrowth ensues. As the condition progresses the cholesterol esters undergo decomposition and liberate fatty acids which, according to Klotz, become

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saponified, insoluble calcium soaps resulting. These precipitate in the deep layers of the intima and eventually lead to the lime deposits which are found in the later stages of the disease.

Most of the authorities on this subject (Marchand, Jores, Aschoff, etc.) have long been in agreement both as to the identity of these earliest changes as well as their significance. It has been definitely established that deposition of cholesterol within the intima is dependent upon a sustained concentration of this substance in the circulating blood and that although other supposed predisposing forces be present, atheromatosis will not develop should the available cholesterol in the blood be insufficient.

The problem thus resolves itself into a determination of the factors which influence the metabolism of cholesterol and which are responsible for its abnormal deposition.

It has long been believed that the development of atherosclerosis is in some way related to disturbances in function among some of the glands of internal secretion. Numerous case reports abound in the literature illustrating such possible relationship. Definite proof of this, however, has been lacking and the present series of experiments were, therefore, undertaken in an effort to throw additional light on the subject.

In consideration of the essential rôle which cholesterol plays in the formation of atheromata I studied the glands of internal secretion which are believed either to control or influence the metabolism of this fatty substance within the body. These tissues include the thyroid, the gonads, the spleen, and the suprarenal. Deficiencies of these organs were created and the relative susceptibility to atheroma formation studied. I wish at this time to present evidence to show the comparative influence of thyroidectomy, gonadectomy, splenectomy, and suprarenalectomy upon the development of experimental atherosclerosis of the aorta. Rabbits were used for the work. Normal animals (i. e., all organs intact), were taken for controls.

The following procedure was followed: In addition to the regular laboratory diet of alfalfa hay, oats, and vegetables, each rabbit was given daily 4 gm. lanolin in 12 cc. cotton seed oil. Lanolin (adepts lanae hyd.) contains large quantities of cholesterol esters.

1. *Controls.* These animals sacrificed after 110 days of lanolin feeding showed early atheromata.

2. *Thyroidectomized Rabbits.* This group was most susceptible. After 40 to 50 days of lanolin feeding these showed moderate atherosclerosis.

3. *Splenectomized Rabbits.* After 50 to 60 days of lanolin feeding this group showed early and moderate atherosclerosis.

4. *Gonadectomized Rabbits.* These showed early atheromata after 50 to 60 days of feeding. The splenectomized rabbits were perhaps slightly more susceptible than this group.

5. *Suprarenalectomized Rabbits.* At least 75 per cent of the main masses were removed from these animals. That they suffered from varying degrees of suprarenal insufficiency was evidenced by the fact that they showed at autopsy lymphoid overgrowth involving thymus and lymph nodes especially. Such rabbits fed between 85 and 100 days showed no atheromata. After 110 days of lanolin feeding others of this group showed early atheromata. It was found, therefore, that rabbits in a state of suprarenal insufficiency were not any more susceptible to the development of atherosclerosis than normals.

TABLE I
Tabulation of Results

Operative Procedure	Period of Lanolin Feeding (Days)	Degree of Atheromatosis	Remarks
None.....	110-120	Early.....	Controls.
Gonadectomy.....	50-60	Early.....	Two fed 50 and 90 days respectively showed no atheromata.
Splenectomy.....	50-60	Early and moderate..	
Thyroidectomy.....	40-50	Moderate.....	
Double Suprarenalectomy..	110	Early.....	Lymphoid overgrowth. Very large thyroids.
Thyroidectomy and Double Suprarenalectomy.....	50	None.....	
Thyroidectomy and Splenectomy.....	50	Severe.....	
Double Suprarenalectomy and Splenectomy.....	45	None.....	
	110	Early.....	
Gonadectomy and Splenectomy.....	100	Severe.....	

DISCUSSION

My studies of the development of the disease confirm the observation that cholesterol deposition within the intima initiates the changes which result in atheroma formation. It is readily produced experimentally by inducing prolonged hypercholesterolemia. I find further that thyroid, spleen, and gonad deficiency each increases the susceptibility of the individual to arteriosclerosis while sublethal suprarenal insufficiency does not. This susceptibility is most marked in the thyroidectomized animals.

These findings are in direct accord with established clinical facts, and it behooves us therefore to seek their explanations. At all events, since cholesterol deposition plays an initial role in the acquirement of the disease we should first seek the mechanisms by means of which the glands under consideration influence the metabolism of this substance within the body.

The spleen appears to be an important storehouse for excess cholesterol. This is well illustrated in cases of prolonged hypercholesterolemia such as is seen in lipemia, especially of diabetic origin, in which splenomegaly is an accompaniment. Arteriosclerosis is constantly found in such cases, even in young children. I observed it in a diabetic girl eleven years old. Also, the relation of the spleen to the reticulo-endothelial system and its function in both the destruction of the old red blood cells and the formation of new erythrocytes emphasizes the additional possibility that the spleen not only stores cholesterol but also utilizes it. Thus, splenectomy alone is followed by hypercholesterolemia. The evidence indicates that deficiency of the spleen predisposes to arteriosclerosis by reason of the deranged cholesterol metabolism which it causes. Thus, one or both of the following mechanisms may be involved when the spleen is removed: absence of a possible storehouse for excess cholesterol; ablation of a tissue which normally utilizes the fatty substance.

Actually little or nothing definite is known concerning the causative relation of the gonads to either disturbed cholesterol metabolism or arteriosclerosis. It is known that these glands do not store the fatty substance in any appreciable amount despite the fact that the interstitial cells become more prominent in long standing hypercholesterolemia. Removal of these sex

glands may give rise to slight elevation of the cholesterol concentration of the blood. This suggests that possibly cholesterol is utilized in ovarian or testicular function. To what extent this is true still remains to be demonstrated. Clinically individuals have been found to develop hypercholesterolemia during the climacteric. It has been emphasized also that indications of atherosclerosis commence to appear most commonly in both sexes during middle or advanced age when sex function has waned. This, however, is not invariably true. The old claim that atherosclerosis is essentially a senile vascular change must be taken with much reservation. The disease has been observed not infrequently even during the second decade of life. On the other hand, William Harvey reported that the celebrated Thomas Parr, who died at the age of 152, had arteries free from evident structural changes. As is true of certain other disturbances, there remains the possibility that individuals who die in old age from the effects of atherosclerosis are those who were fortunate enough not to have succumbed to this disease during younger life.

Much emphasis has been placed on the coexistence of high blood pressure and atherosclerosis. Indeed, many authors claim that there is a causative relationship between the two. I shall not discuss this question at the present time, for it would be necessary to deal with it at great length, which would lead us beyond the scope of this paper. Suffice it to mention the facts that hypertension may exist for a long time without an accompanying atherosclerosis and that severe atherosclerosis may develop in the presence of normal blood pressure. I demonstrated this experimentally in animals in 1925.

There remains another possibility: the synergistic functional interrelationship which operates between the gonads and the thyroid. It is illustrated in the finding that gonadectomy is followed by a slight drop in heat production and, in some instances, involution of the thyroid. Also, at those periods when the sex glands are the seat of both physiological and morphological alterations (puberty, pregnancy and lactation, menopause), the thyroid may likewise undergo striking changes, sometimes to abnormal degrees, so that simple goiter, exophthalmic goiter or myxedema may result. It appears, therefore, that the gonads affect the utilization of cholesterol through the

functional interrelationship which operates between the sex glands and the thyroid.

The thyroid, on the other hand, plays a more direct and essential role in the metabolism of the fatty substances, including cholesterol. It appears that thyroxine is necessary for the complete oxidation of fats in the body. This is evidenced by the finding that high fat diets cause increased thyroid activity, eventually leading to thyroid overgrowth (goiter) (Marine and Lenhart, McCarrison). In a series of experiments done with Dr. E. J. Bauman I have observed further that such thyroid hyperplasia produced by feeding neutral fat is accompanied by hypercholesterolemia, and that this increase in cholesterol concentration in the blood is directly proportional to the degree of thyroid insufficiency as indicated by hyperplasia. Illustrative data are given in table 2. Photograph 5 shows thyroid overgrowth resulting from prolonged high fat, iodine-free feeding.

TABLE II

Rabbit Number	Daily Feedings	Blood Cholesterol After 40 Days Fat Feeding (mg.)	Thyroid After 40 Days	Blood Cholesterol After 120 Days (mg.)	Thyroid After 120 Days	Remarks
I	Cotton seed oil—12 cc.	77	Normal—early hyperplasia	133	Moderate—marked hyperplasia	Iodine—free diet
II	Cotton seed oil—12 cc.	130	Moderate hyperplasia	109	Marked—hyperplasia	Iodine—free diet
III	Cotton seed oil—12 cc.	96	Moderate hyperplasia	149	Marked—hyperplasia	Iodine—free diet
IV	Cotton seed oil—12 cc.	117	Moderate hyperplasia	199	Marked—hyperplasia	Iodine—free diet
V	Cotton seed oil—12 cc.	86	Normal—early hyperplasia	92	Moderate—hyperplasia	Iodine—free diet
VI	Cotton seed oil—12 cc.	94	Moderate hyperplasia	127	Marked—hyperplasia	Iodine—free diet

Thus, when the thyroxine supply is subnormal, as occurs in thyroid insufficiency, the fats and fatty substances are only incompletely oxidized. This gives rise to hypercholesterolemia, cholesterol deposition and atheroma formation. In this manner thyroid deficiency predisposes to atheromatosis.

Disturbed suprarenal function has been believed by some authors to bear a causative relationship to the development of atherosclerosis. Some are of this opinion by reason of the fact

that repeated epinephrin injections in animals have been shown to produce degenerative lesions in the arterial wall. These have erroneously been classed with atherosclerosis. Actually the epinephrin lesions are localized necroses of the media (similar to Mönckeberg's sclerosis) while atheromata, as has already been pointed out, are aggregate swellings resulting from fatty deposits and cellular overgrowth and confined primarily to the intima. Klotz, who described the epinephrin effects, recognized this difference, but some authors seem to have lost sight of the fact.

Cases have also been reported supposedly illustrating the possibility that certain abnormalities in the suprarenal cortex (interrenal gland) may be responsible for the arterial lesions which were present. These cases showed clinically pronounced hypertension and at necropsy cortical adenomata in one or both of the suprarenal glands and generalized atherosclerosis. The exact mechanism nobody has ventured to try to make clear. However, the inference to be drawn is that the presence of cortical adenomata signifies overactivity of this portion of the suprarenal gland and as destruction of the interrenal may give rise to an Addisonian complex with hypotension and lymphatism, so conversely should excessive function of this gland produce hyperpiesia and atherosclerosis. There are so many fallacies in such an hypothesis that it would take too long merely to enumerate them. Suffice it to point out that such adenomata may exist without any indication of either hypertension or atherosclerosis. Indeed, I have frequently found them in suprarenals obtained from young, healthy animals during my work in the laboratory and in abattoirs. There is not a scintilla of evidence to show that there is any relation between the presence of cortical adenomata of the suprarenal and either hypertension or atherosclerosis.

Still another function has been ascribed to the suprarenal cortex through the agency of which disturbances in its function are believed to influence cholesterol metabolism and, in turn, consequent atheroma formation. The French school, led by Grigaut, claim that this gland controls the metabolism of cholesterol; the Germans, under the leadership of Aschoff and his pupils, maintain that it is a storehouse for cholesterol. If either of these beliefs were true, an individual in a state of suprarenal insufficiency should present evidences of disturbed cholesterol

metabolism. This, it has been demonstrated, does not occur until the animal has become moribund, during which brief period the blood is concentrated (Bauman). My results are in accord with the latter. I find that rabbits in a state of sublethal suprarenal insufficiency are not more susceptible to hypercholesterolemia and arteriosclerosis than normal animals.

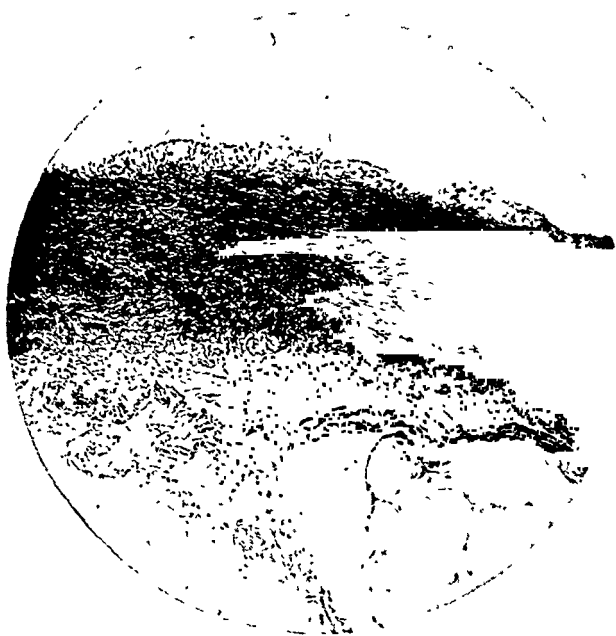
In four instances (one thyroidectomized and 3 splenectomized) I obtained evidence which suggests that a state of suprarenal insufficiency exerts an inhibitory influence upon the development of arteriosclerosis. This observation coincides with certain facts well known to pathologists for almost a century, and during the present era being emphasized by workers studying the relation of certain constitutional states to the acquirement of disease. In conditions characterized by lymphoid overgrowth such as status thymicolymphaticus and lymphatism arteriosclerosis is comparatively rare. The hearts and aortas of such individuals are known to be characteristically small and "hypoplastic." This was recognized clinically during the early part of the last century in England by the pathologist Burns, and after him in France by Parrot. There are various other features which typify this constitutional state, but I shall merely mention the outstanding anomaly, overgrowth of the lymphoid tissue throughout the entire body. This sometimes occurs to the extent of lymphocytic infiltration within the various tissues such as the heart muscle, thyroid, etc. In addition there is striking enlargement, due either to regeneration or persistence of the thymus gland.

In sublethal suprarenal insufficiency experimentally produced, such as in the animals described in these experiments, an identical anomaly appears to develop. Such animals I find, contrary to the beliefs of the French and German schools, are not more susceptible to the development of hypercholesterolemia and arteriosclerosis than normal animals. Furthermore, it is suggested that a state of interrenal insufficiency may exert an inhibitory influence upon the acquirement of arteriosclerosis.

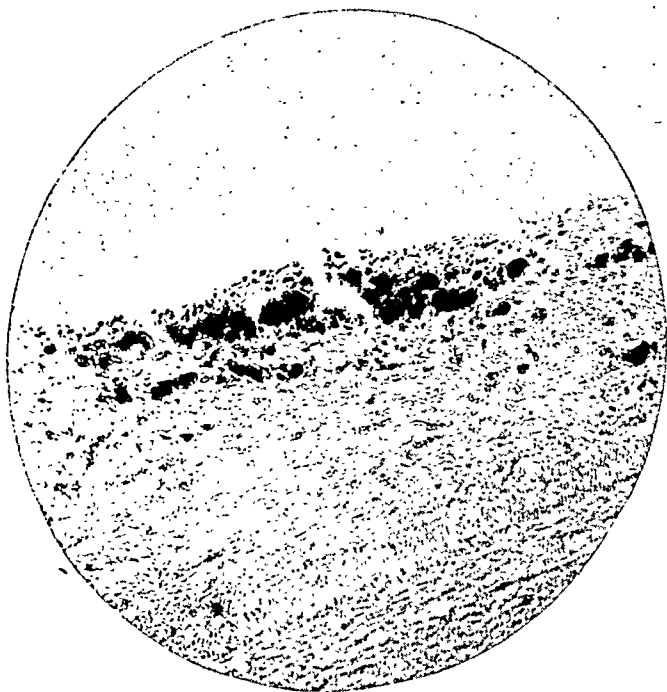
SUMMARY

The data herein offered indicate that deposition of cholesterol within the intima initiates the formation of atheromata.

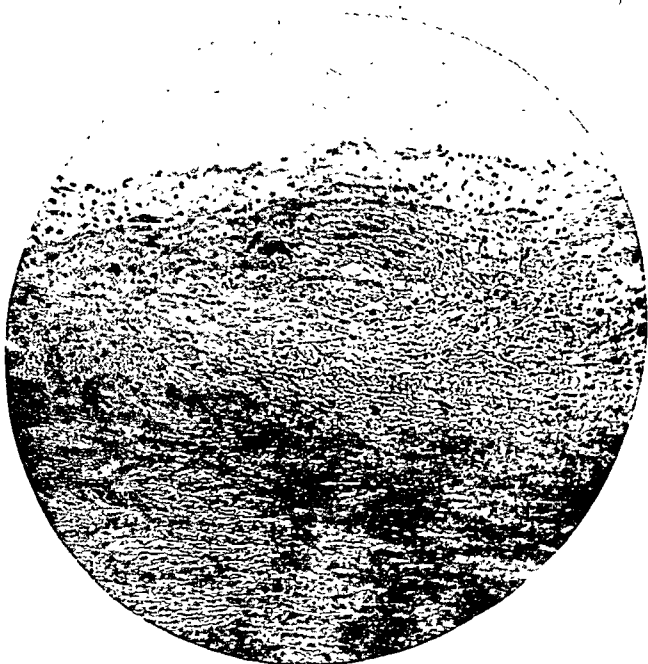
Any condition which causes or facilitates such deposition thereby predisposes to the development of atherosclerosis. Deficiency of the thyroid, spleen or gonads each augment hypercholesterolemia and thereby accelerate the consequent formation of atheromata. Suprarenal insufficiency, on the contrary, does not facilitate the development of hypercholesterolemia or atherosclerosis.



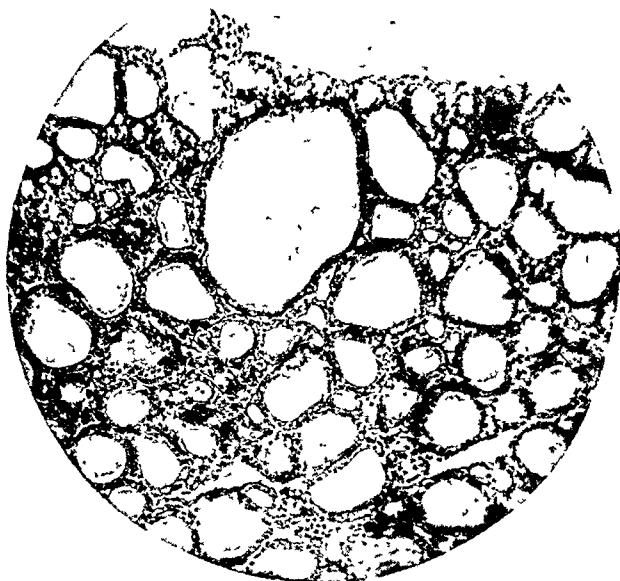
No. 1.—Shows atheromata of rabbit aorta, experimentally produced. Low power, hematoxylin and eosin stain, celloidin section.



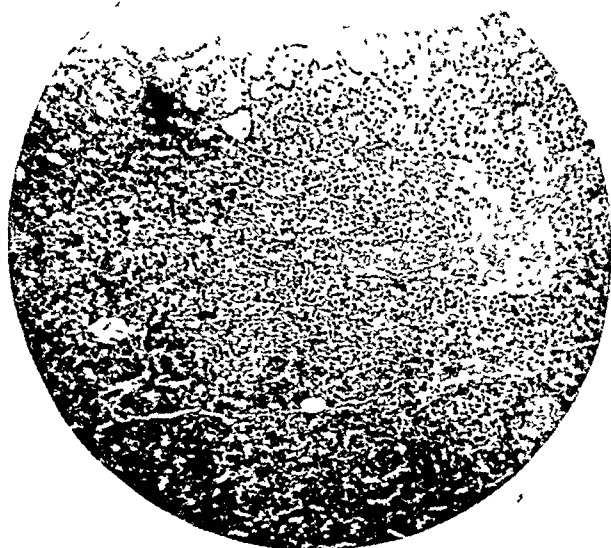
No. 2.—Shows deposition of fatty substances in deep strata of intima. Frozen section, Sudan III fat stain, high power, human aorta.



No. 3.—Shows large vacuolated cells in intima which have taken up fatty material. Human aorta. Paraffin section. Hematoxylin and eosin stain. High power.



No. 4.—Snip of rabbit thyroid before feeding high fat iodine-free diet. Low power. Celloidin section. Hematoxylin and eosin stain.



No. 5.—Snip of rabbit thyroid after 120 days high fat iodine-free diet (see text). Note the extreme degree of hyperplasia and vascularization. There are a few follicles along the periphery. Celloidin section. Hematoxylin and eosin stain. Low power.

THE REPLACEMENT OF THE SERUM CALCIUM AND THYROID GLAND IN RABBITS AFTER INTRA-VEINUS INJECTIONS OF OXALATE*

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In recent years a considerable amount of evidence has been obtained indicating that a normal calcium content of the blood is an important factor in the resistance of the animal to disease. It has been shown by the writer (1), by Scott (2) and by others that in a number of chronic conditions, associated especially with infection, the serum calcium is decreased and that clinical improvement often accompanies its return to normal. But it has also been found that the administration of thyroid gland in these cases is followed by a new lowering of the serum calcium and a clinical relapse.

The following experiments were carried out with a view to determining the rapidity with which calcium is mobilized from the tissues to the blood-stream following the injection of oxalates, and also the effect which thyroid extract might have upon the rate of calcium replacement.

Ammonium oxalate was injected intravenously into rabbits and at successive intervals of ten minutes blood samples were taken from the ear vein, and the calcium content of the serum estimated by the method previously described by the writer (3).

In Table 1 are shown the results obtained after single injections of oxalate.

TABLE I

Rabbit's Weight, kgm.	Calcium Equivalent of Oxalate Dose, mgm.	Time Taken for Serum Calcium to Become Normal, mins.	Calcium Replaced per Min. per Kgm., mgm.
3.1	5.0	20	0.080
	5.0	20	0.080
	10.0	45	0.072
2.4	4.0	20	0.083
2.0	6.4	40	0.080
1.3	5.2	55	0.073

The figures in the second column show that amount of calcium which would combine chemically with the amount of am-

* This work was carried out under the Foulerton Committee of the Royal Society.

monium oxalate injected. It is seen that in all cases the amount of calcium replaced per minute per kgm. is relatively constant, and is of the order of 0.08 mg. The rate of replacement is a function of the initial oxalate dose per kgm.

In the next two experiments repeated doses of oxalate were given at ten-minute intervals, and a blood sample was taken five minutes after each dose.

TABLE II

Weight of rabbit=2.3 kgm.

Time mins.	Change in Serum Calcium, mgm.	Calcium Equivalent of Oxalate Dose, mgm.	Calcium Replaced, per Min. per Kgm. mgm.
0-10	-1.0	0.8	0.
10-20	-0.5	0.8	0.013
20-30	-0.4	0.8	0.017
30-40	-0.2	0.8	0.026
40-50	0.	0.8	0.035
50-60	+0.3	0.8	0.048
60-70	+0.5	0.8	0.056
70-80	+0.8	0.8	0.076

The serum calcium returned to its normal level in eighty-four minutes. The amount of calcium replaced for each time interval is calculated as the algebraic sum of the figures in the second and third columns, the minus signs in the second column indicating a fall and the plus signs a rise in the serum calcium. Since the total oxalate given is here equivalent to a loss of 6.4 mgm. of calcium, it is evident that replacement is slower when repeated small amounts are injected than when an equivalent single dose is given. From Table 1 a single dose of the same size should be replaced in less than forty-five minutes, in a rabbit of the same size.

A similar experiment was carried out using twice the amount of oxalate at each dose.

TABLE III

Weight of rabbit=2.4 kgm.

Time, mins.	Change in Serum Calcium, mgm.	Calcium Equivalent of Oxalate Dose, mgm.	Calcium Replaced per Min. per Kgm., mgm.
0-10	-1.4	1.6	0.
10-20	-1.2	1.6	0.017
20-30	-0.4	1.6	0.051
30-40	0.5	1.6	0.087
40-50	+1.2	1.6	0.120
50-60	+1.4	1.6	0.125

The serum calcium returned to normal in sixty minutes. It is evident therefore that doubling the dose of oxalate has considerably increased the rate of calcium replacement. The average rate of replacement over the whole period is 0.08 mgm. per minute per kgm., whereas in the previous experiment it was 0.038 mgm. The rate of replacement is, therefore, directly proportional to the oxalate dose under these conditions. When the oxalate dose was again doubled the serum calcium fell continuously, indicating that the rate of replacement could not be accelerated any further. It would therefore seem probable that a rate of 0.125 mgm. per minute per kgm. is maximal.

It may be noticed in Tables 2 and 3 that the highest replacement rates occur some time after the beginning of the experiment. Where a single dose of oxalate is given, however, the highest replacement rates occur immediately after the injection.

TABLE IV

Weight of rabbit, kgm.....	3.1	2.0	2.4
Calcium equivalent of oxalate dose, mgm....	10.0	6.4	4.0
Time intervals— 0-10.....	0.	0.110	0.083
10-20.....	0.119	0.080	0.080
20-30.....	0.103	0.070
30-40.....	0.080	0.060
40-50.....	0.065

The figures given are the replacement rates for the corresponding time intervals.

THE EFFECT OF INJECTIONS OF THYROID EXTRACT

Another series of rabbits was treated with single doses of oxalate together with a watery extract of thyroid gland intravenously, with the following results:

TABLE V

Weight of Rabbit, kgm.	Thyroid Dose, mg. per kgm.	Calcium Equivalent of Oxalate Dose, mgm.	Time Taken for Serum Calcium to Become Normal, mins.	Calcium Replaced per Min. per Kg., mgm.
1.6	15	5.3	50	0.066
2.4	30	4.0	40	0.042
2.7	30	8.0	90	0.033
2.0	30	6.4	100	0.032
2.1	30	6.4	100	0.030

Comparing these results with those shown in Table 1, it is seen that the injection of thyroid extract lowers the rate of calcium

replacement considerably, and there is some evidence that the degree of slowing is proportional to the amount of thyroid extract injected.

The rates of calcium replacement over short time periods under the influence of thyroid extract are shown in Table 6, and they may be contrasted with those in Table 4. Single doses of oxalate were used.

TABLE VI

Weight of rabbit, kgm.....	1.6	2.4	2.0	2.1
Calcium equivalent of oxalate dose, mgm....	5.3	4.0	6.4	6.4
Thyroid dose, mgm. per kgm.....	15	30	30	30
Time intervals— 0-10.....	0.	0.	0.	0.
10-20.....	0.044	0.	0.	0.
20-30.....	0.075	0.02	0.	0.
30-40.....	0.106	0.07	0.	0.
40-50.....	0.100	0.134	0.	0.
50-60.....	0.020	0.028
60-70.....	0.030	0.030
70-80.....	0.035	0.040
80-90.....	0.055	0.060
90-100.....	0.100	0.090

These results suggest that there is an inhibition of the movement of calcium from the tissues to the blood-stream. That the inhibitory effect is due to the thyroid extract seems evident, since in the first place it did not occur in Table 4, where no thyroid was used, and in the second it is less in the first rabbit in Table 6 than in the third; in these the oxalate dose per kgm. was the same, but the thyroid dose in the first instance was half that in the second. The total duration of the period of inhibition appears to depend on both the amount of oxalate and of thyroid injected. It is also seen that the maximal replacement rates do not occur immediately after the oxalate dose, as in Table 4, but are similar to those in Tables 2 and 3, where repeated oxalate injections were used.

If thyroid extract produces this apparent inhibition of calcium replacement in the serum by causing a retention of calcium in the tissues, it should cause a diminution in the serum calcium when injected without oxalate. Two rabbits were treated with 30 mgm. of thyroid extract per kgm. intravenously, and in both cases a definite reduction in the serum calcium was obtained. In the first case the serum calcium did not return to its normal level for 120 minutes, and no apparent attempt at replacement of the deficiency occurred for 80 minutes. When the normal

level had been reached, an oxalate dose equivalent to the loss of 6.3 mgm. of calcium was given. The serum calcium became normal in 45 minutes, giving an average replacement rate of 0.073 mgm. per min. per kgm. This is a practically normal value and confirms the fact that the thyroid effect had passed off. In the second rabbit a single dose of oxalate, equivalent to a loss of 9.2 mgm. of calcium, was given half-way through the supposed period of thyroid inhibition. The serum calcium returned to normal in 70 minutes, giving an average replacement rate of 0.043 mgm. per min. per kgm. This is a lowered rate, comparable with those shown in Table 5, and it confirms the fact that the thyroid effect had not yet passed away. Leicher (4) noted that in man thyroid feeding lowered the serum calcium and that a marked decrease occurred in *exophthalmic goitre*.

The two experiments just recorded indicate that for the dose of thyroid extract used, the period of inhibition of calcium replacement extends up to eighty minutes. The results shown in Table 6, where thyroid and oxalate were injected together, all show a shorter period of thyroid inhibition. This suggests the possibility that the oxalate stimulates the mechanism of calcium replacement, so that the thyroid effect is partially overcome. It seems possible that the rapid adjustment of the calcium content of the plasma is controlled by two separate mechanisms; the one decreasing the loss from the tissues and dependent upon the thyroid, and the other increasing the loss from the tissues and dependent upon the parathyroid glands.

COMMENT

From the results which have been recorded it would seem probable that the fall in the serum calcium and the clinical relapse which may occur following the use of thyroid gland in the pathological conditions previously referred to, are due to the inhibitory action of the thyroid preparation upon the rate of calcium replacement in the patient's plasma.

The results shown in Table 2 suggest by analogy that in chronic infective states in which there is a slight calcium deficiency and a minimal systemic reaction, the rate of calcium replacement will be low. This analogy is to some extent confirmed by the clinical observations in cases of chronic ulceration and other diseases (1).

In acute febrile conditions there are two factors to be considered. The first is the rapid loss of calcium from the plasma, indicated by the increased calcium excretion and by the liability to tetany when a deficient calcium metabolism pre-exists. This will lead to a rapid rate of calcium replacement, since it has been shown that within certain limits the rate of calcium replacement varies as the degree of decalcification. But on the other hand, the acute febrile reaction is largely conditioned by an increase in the activity of the thyroid. This would tend to slow the rate of calcium replacement in the plasma by inhibiting the release of calcium from the tissues. The maintenance of an effective calcium tension in the plasma in acute conditions will thus come to depend largely upon the degree and duration of the febrile response to the infection. For it is seen in Table 5 that:

1. A large oxalate dose and a small thyroid dose reduce the replacement rate but slightly;
2. A small oxalate dose and a large thyroid dose cause a marked delay;
3. A large oxalate dose and a large thyroid dose cause a very considerable delay.

This would suggest that when the febrile reaction is brief and not too severe, the replacement rate may not be greatly reduced, but when the reaction is severe, prolonged and without intermission, the rate of replacement will be depressed.

It follows therefore that in chronic infective states in which the rate of calcium replacement is low, the production of single acute febrile attacks of brief duration and with a proper period between them for recovery, should be a means of accelerating the calcium replacement rate. If, as would seem probable, there is any relation between the calcium tension of the plasma and the ability of the animal to resist the organism infecting it, then the production of such acute reactions should be beneficial, since their end-result would be an acceleration of the calcium replacement rate. It would seem possible that the use of non-specific protein therapy and to some extent the use of vaccines may be instances of a beneficial reaction of this type.

Conversely, the increment of the calcium content of the plasma, either by calcium injections or by parathyroid therapy, should cause an exacerbation of the chronic infection. Examples

of this type of reaction have been frequently observed in the treatment of chronic infections with parathyroid gland or with calcium solutions (5).

CONCLUSIONS

1. The intravenous injection of oxalate into rabbits is followed by a rapid replacement of the calcium removed; with a single oxalate dose the average replacement rate is of the order of 0.08 mgm, per minute per kgm.

2. If the oxalate is given in small repeated doses the rate of replacement varies as the oxalate dose. Under these conditions there is evidence that the replacement rate does not rise above 0.125 mgm. per minute per kgm.

3. The injection of thyroid extract causes a lowering of the replacement rate, apparently due to an inhibition of the release of calcium from the tissues. The degree of the thyroid effect is proportional to the dose.

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STUDIES OF THE THYROID APPARATUS, XLIX. WATER BALANCE IN CONDITIONS OF THYROID AND PARATHYROID DEFICIENCY

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An examination with respect to water percentage and refractive index was made of the blood serum of the thyroidless and parathyroidless rats, and their litter mate controls, the growth of which in body and organ weight has been the subject of the preceding papers of this series. This was done in order to provide data for a study of the influence of the glandular deficiencies on water balance within the organism. Since it was recognized that these records alone would afford but scanty material for a generalization, four other organs were systematically investigated, namely: the brain, the spinal cord, the humerus, and the femur. As will appear, the data obtained from these five tissues are strikingly consistent.

The plan and scope of the investigation as a whole (Hammett, 1923a), the number and distribution of the rats (Hammett, 1926a), and the methods of collecting and analyzing the blood (Hammett, 1923b), and tissues (Hammett, 1924a, 1923c), are described in earlier papers.

In table 1 is given the observed mean water percentage of the blood serum of the several groups of animals.

Before going on to the main theme of the paper, a comparison of the control (normal) values with those obtained by Hatai (1918) from a different series of rats raised under different dietary and environmental conditions is in order.

The figures in table 1 (first column) confirm Hatai's finding that the water percentage of the blood serum decreases with age. This shift also occurs in the central nervous (Hammett, 1926b; Donaldson, 1916), and skeletal (Hammett, 1925; Donaldson and Conrow, 1919), systems; indeed, throughout all living nature. The phenomenon is not due to an absolute loss of water from the organism, for growth is everywhere accompanied by an in-

TABLE I

OBSERVED MEAN WATER PERCENTAGE OF THE BLOOD SERUM OF THE SEVERAL GROUPS OF RATS

MALES					
Age in Days	Reference Controls	Thyroidless*		Parathyroidless*	
		Controls	Tests	Controls	Tests
	%	%	%	%	%
23.....	94.57±0.08	91.92±0.07	91.50±0.12	92.10±0.04	92.07±0.07
30.....	94.24±0.05	91.95±0.08	91.71±0.07	91.76±0.07	91.85±0.08
50.....	93.42±0.07	91.92±0.09	91.77±0.10	91.94±0.10	91.83±0.07
65.....	92.50±0.10	92.00±0.13	91.89±0.10	91.95±0.12	91.89±0.06
75.....	92.69±0.09	91.89±0.05	91.73±0.09	91.81±0.08	92.10±0.10
100.....	92.37±0.05	91.89±0.03	91.53±0.06	91.89±0.03	91.94±0.06
FEMALES					
23.....	94.12±0.07	92.03±0.11	91.87±0.06	91.97±0.06	92.07±0.07
30.....	94.30±0.07	91.87±0.08	91.88±0.08	91.98±0.06	91.99±0.06
50.....	93.40±0.07	91.88±0.09	91.66±0.11	91.74±0.10	91.88±0.04
65.....	92.47±0.09	91.90±0.08	91.98±0.09	91.74±0.10	91.98±0.04
75.....	92.55±0.08	91.63±0.08	91.67±0.13	92.00±0.05	91.87±0.05
100.....	92.08±0.21	91.92±0.10	92.08±0.10	91.92±0.21	91.94±0.08

*At 150 days of age.

crement in water mass. It is rather due to the fact that the incorporation of solids into the growing organism goes on at the faster rate.

Now it is obvious that body substance constitutes, within limits, a measure of reserve capacity for adjustment to untoward environmental conditions. Hence the solids-water differentiation with age is but the resultant of the evolutionary trend to the attainment of maximum capacity for adjustment to a continuously changing environment. The mechanism of the process, as at present exhibited, has yet to be analyzed.

Hatai (1918) observed that an irregularity in the age curve of water percentage of the blood serum was produced, as might have been predicted, by the adjustment to the new diet consequent on weaning. This is confirmed in my records. The data for the tissue reaction are inconstant. It is probable, however, that the use of a narrower interval between observations over

this period of change, and larger numbers of animals, would show the distortion as general.

Hatai's (1918) finding that the age curve of the water percentage of the blood is distorted at the onset of sexual maturity (65-75 days of age), is confirmed by my figures. Records from the humerus, femur, brain and spinal cord show a like irregularity at this stage of development (Hammett, 1925, 1926b). From this it may be assumed that the reaction is general and not peculiar to the blood. Simple reflection on the commonly observed physical alterations should make obvious the conclusion that the increment in gonadal incretory activity which takes place at puberty initiates profound changes in the chemical processes of the body. That the water balance should be distorted under these conditions is not surprising. What is unexpected is the fact that the phenomenon has not received the study it deserves from the biological point of view.

Hatai (1918) tentatively postulated a sex difference in water percentage of the blood, the direction of which shifts with the attainment of sexual maturity. My records show no such shift. They do indicate, however, that the values are generally higher in the male. This difference is also found in the four other organs (Hammett, 1925, 1926b). Because all five sets of observations were made on the same animals, kept under identical conditions of diet and environment, the validity of the difference is unquestionable. It is not due to sex difference in gonadal incretory activity.

Now growth capacity and water percentages decrease simultaneously with advancing age (Hammett, 1926c). This fact suggests a relationship between the processes concerned in the two phenomena. Moreover, the higher water percentage in the male is associated with the higher growth capacity. Thus the direction of sex difference is consistent with that of the age difference. From this the assumption is justified that the sex difference in growth capacity is a factor in the determination of the sex difference in water percentage.

To summarize: it is evident that the processes concerned in the regulation of the water balance within the body are fundamentally related to those concerned in physiological development. Puberty, the aging of the organism, sex, and the change which occurs in the character of the diet at weaning are all

normally occurring factors in development, and each has its characteristic influence. Any study of water balance which aims at completeness must take them into account. The mechanisms by which these factors bring about the observed changes are worthy of investigation.

We can now turn to the influence of thyroid and parathyroid deficiency on water balance. The earlier work pertinent to the study has been reviewed elsewhere (Hammett, 1923b, 1923d).

Now the growth of the test rats has been retarded by the glandular deficiencies (Hammett, 1926c). The rats are smaller and less developed than their litter mate controls of the same age and sex. From what has gone before it is evident that this retardation of development might of itself be productive of differences in water percentage value between tests and controls. It would lead to the appearance of a higher percentage of water in the blood serum of the tests. Such indeed is found in some of the parathyroidless groups, as seen from table 1. If the glandular deficiencies likewise produced an effect, differences of unpredictable direction might be obtained. That such occur is seen from the fact that the water percentages of the thyroidless groups tend generally to be less than those of their controls of the same age and sex. Comparison of these absolute values is obviously inadequate. It is necessary to bring the data to a common level. This is best effected by comparing the values observed in the tests with those of normal animals of the same body weight as the tests. This is done by charting the observed values of water percentage of the controls on body weight; locating the expected values on this curve according to the body weight of the tests, and noting the divergence of the observed water percentage values of the tests therefrom. In the case of the brain, spinal cord, humerus, and femur, organ weight is preferred and used instead of body weight as the basis of comparison.

In this way the weight variable, which is taken as an index of growth, is stabilized for. The end-result, while admittedly an approximation, is nevertheless, within limits, a valid index of the direction and degree of deviation of the tests from their controls. The results are given in table 2.

It is at once evident that the glandular deficiencies produce an organism in which the water percentage is less than that of

an animal of the same degree of mass development. In the growth that has occurred the increment in water has been a less than normal proportion. In other words, the water balance has been upset in the direction of anhydremia. This generalization is permissible from the fact that three systems of widely divergent character show the same type of response. The exceptions in the skeletal system of the parathyroidless females are due to a sex-specific sensitivity to the disturbance in calcium exchange. This is discussed in another place (Hammett, 1927a, 1927b).

TABLE II

THE DIFFERENCE BETWEEN THE OBSERVED AND THE EXPECTED PERCENTAGES OF WATER IN THE BLOOD SERUM, BRAIN, SPINAL CORD, HUMERUS AND FEMUR OF THE SEVERAL GROUPS AT 150 DAYS OF AGE

Age Series	Blood Serum		Central Nervous System				Skeletal System			
			Brain		Spinal Cord		Humerus		Femur	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
THYRO-PARATHYROIDECTOMIZED										
23	−0.70	−0.22	−0.06	+0.12	−0.27	−0.22	+0.6	−5.8	−0.1	−3.2
30	−0.60	−0.41	−0.12	−0.45	−0.24	−0.30	−2.5	−5.5	−3.1	−3.3
50	−0.52	−0.89	−0.14	−0.73	−0.25	−0.64	−2.6	−5.0	−3.1	−6.8
65	−0.39	−0.09	−0.13	−0.25	−0.19	−0.30	−2.1	−6.4	−5.0	−5.9
75	−0.52	−0.62	−0.19	−0.78	−0.26	−0.83	−1.0	−0.4	−3.0	−1.0
100	−0.73	−0.07	−0.12	−0.41	−0.21	−0.26	−3.7	−3.0	−4.7	−2.2
Av.	−0.58	−0.38	−0.13	−0.42	−0.24	−0.43	−1.9	−4.4	−3.2	−3.7
PARATHYROIDECTOMIZED										
23	−0.20	−0.03	+0.01	−0.06	+0.24	+0.09	+0.9	+2.9	+1.3	+5.5
30	−0.32	+0.03	0.00	−0.08	−0.09	−0.11	+0.5	+0.8	+0.4	+2.1
50	−0.43	−0.25	−0.24	−0.12	−0.11	−0.18	−1.6	−0.3	−1.2	+0.4
65	−0.45	−0.12	−0.35	−0.16	−0.33	−0.29	−2.7	−0.8	−3.5	+0.2
75	−0.44	−0.29	−0.11	−0.31	−0.10	−0.8	+0.8	−1.5	+0.2
100	−0.28	−0.12	−0.07	−0.07	+0.05	−0.01	−2.3	+0.3	−3.5	+0.6
Av.	−0.35	−0.13	−0.13	−0.10	−0.09	−0.10	−1.0	+0.6	−1.3	+1.5

There is to be found in the literature the implication that water balance is specifically related to thyroid function. On the surface, these observations would seem to indicate that this is true. But I believe the conclusion is not a precise statement of the relation. I do not believe that thyroid activity has any direct bearing on water balance. Rather do I believe that the distortions observed, both in conditions of thyroid deficiency and thyroid excess, are secondary reactions consequent on the lowering or raising of the metabolic level which results from the decrease or increase in thyroid stimulation. More definitely, I believe that they are fundamentally based on the shifts in the nutritional level brought about by the shifts in thyroid activity as discussed in an earlier paper (Hammett, 1926a).

Without going into repetitive detail it may be stated that the cumulative evidence of the growth studies indicates that, with few exceptions, the growth retardation observed in conditions of thyroid deficiency is largely attributable to the general lowering of the effectiveness of the growth processes of the body as a whole, due to the lowered nutritional level resulting from the reduction in metabolic rates, rather than to any specific growth relation to thyroid activity as such. In conditions of parathyroid deficiency the growth retardation is likewise due to a lowering of the nutritional level. The basis of this has been discussed in the paper referred to above.

If this hypothesis is true it would be expected that the direction of distortion of water balance would be the same in the thyroidless as in the parathyroidless animals. Such is seen to be the case. This similarity in type reaction immediately throws doubt on the idea that water-balance and thyroid activity are specifically related. It is further weakened and the alternative hypothesis strengthened by the fact (as should be expected if the latter is true), that the parathyroidless group of lesser growth retardation shows the lesser degree of deviation in water percentage from the normal. There is even a fair but significant concordance of fact and theory in the case of the sex differences in degree of divergency. Moreover, if the hypothesis is well founded, it would be expected that the direction of deviation of the water percentage would be the same as that observed in fasting. From the results of Hatai (1918), the literature he quotes,

and that reviewed by Jackson (1925), it is seen that the reactions are identical.

The data are consistent. They support the belief that the anhydremic trend observed in conditions of thyroid and parathyroid deficiency is largely due to the lowered nutritional level, and not to any specific relation of the water-balance to the activity of the glands in question.

A possible secondary factor of importance is a disturbance of the temperature regulating mechanisms. It is a matter of common knowledge that increased sensitivity to cold and tendency to a sub-normal skin temperature may be accompaniments of under-nutrition (Benedict and Roth, 1918). As would be expected, the same is true in conditions of hypothyroidism (MacKenzie, 1926; Sajous, 1918; Korenchevsky, 1926). Barbour and Hamilton (1924) observed that blood concentration occurs in conditions of exposure to environmental cold, that the cold anhydremia is due to loss of fluid from the blood-stream (Barbour and Hamilton, 1925), and that "the fluid which leaves the blood in the regulation of the body against a cold environment is diverted to the cooled skin, subcutaneous tissue and muscles. In these structures it helps insulate the deep-lying tissues" (Hamilton and Barbour, 1925).

These several observations immediately suggest the idea that an initial stage in the production of the cutaneous symptoms of myxedema is a shift in water from the blood and deeper-lying tissues to the surface structures in response to a disturbance of temperature regulation. The latter changes could well result from an impairment of the nutritive capacity as pointed out by Adami (1910). While myxedema is presumably characteristic of thyroid deficiency, there is also a well-recognized edema of undernutrition (Jackson, 1925). It has yet to be proved that the latter may not have the potentiality of development into the former type of pathological alteration. Whether this may occur or not, it is clear that the similarities far outweigh the dissimilarities, and the principle of the hypothesis that the trend to anhydremia, in the thyroidless as well as in the parathyroidless rats, is essentially based on a condition of virtual undernutrition, is nicely sustained by these data from other sources.

In earlier papers (Hammett, 1923b, 1923d) a comparison was made of the slopes of the linear relation between the refractive index and water percentage of the blood-serum in the 75 and 100 day old series. From the results there obtained the conclusion was drawn that the glandular deficiencies induced a disturbance in the nature or distribution of the refractive substances other than water. A like treatment of the data from all the age series has brought out the fact, however, that no consistent differences are demonstrable. Hence the earlier conclusion must be withdrawn and the answer to the question left in abeyance.

SUMMARY

Puberty, advancing age, sex, and the change in diet which occurs at weaning are all normal developmental factors which influence the water balance of the mammalian organism.

Thyroid and parathyroid deficiency studied in an extensive series of male and female rats was found to produce a definite tendency to anhydremia in the central nervous system, blood, and skeletal system. This is attributable to the lowered nutritional level brought about by these conditions, rather than to a direct or specific influence of glandular activity on water balance.

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THE EFFECTS OF TESTICULAR SUBSTANCE IMPLANTATIONS ON GLYCOSURIA

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Since 1918 experiments have been carried on at the California State Prison at San Quentin with the engrafting of the testes and with the implantation of testicular substance in prisoners confined in the institution.

In some who were afflicted with diabetes it was noticed that there was a diminution and in some cases a complete disappearance of sugar in the urine following one or more testicular substance implantations.

One patient, age 67, having had diabetes for nine years, was, on February 8th, 1921, six days after entrance to prison, given an implantation of 4.0 grams of fresh goat's testes under the skin of the abdomen.* His subjective symptoms improved and he felt better in that the cramps in his legs were fewer and his sleep was better. On May 25th, he received a second testicular substance implantation. It was noted that the urine following this had a moderate amount of sugar, no quantitative test having been made. The patient was transferred to Folsom Prison, one hundred miles distant, in August, 1921. The Resident Physician, Dr. J. D. Rogers, made the following urine reports:

August 10, 1921.....	No sugar
August 13, 1921.....	Traces of sugar
December 9, 1921.....	No sugar
January 9, 1922.....	No sugar
April 9, 1922.....	Traces of sugar
June 19, 1922.....	No sugar

No dietary restrictions had been made and at Christmas the patient partook of holiday pastries and candies. The noteworthy observation in this case was that the patient was sugar free on dates when tests were made during a period of about ten months subsequent to subcutaneous injections of testicular substance.

A somewhat similar case was that of an Italian, age 51 years. He had had diabetes for two years and had been under medical

*The technic is described in this Journal, 1922, 6, 787-794.

treatment during this time previous to his entrance on December 26th, 1923. Daily tests of his urine showed sugar ranging from 2.3 to 3.8 per cent. On January 17th, 1924, he was given a testicular substance implantation. The amount of sugar steadily decreased and at the end of sixteen days none could be found. A second implantation was given June 8th, a third on August 10th, and a fourth on October 20th. No dietary restrictions were made, the food being the same before the implantation as that following. Except for the period between August and October when he ranged from one to four per cent, with an occasional free day, there was no sugar in the urine and none re-appeared during the period from October 20th, 1924 to January 20th, 1925, when the patient was released.

A third subject, J. M., age 65, was received at San Quentin on February 2nd, 1924, with a diagnosis of diabetes mellitus of one year's duration. Daily tests of his urine showed 2 per cent sugar. On March 6th, he was given an implantation of testicular substance. By March 11th, the sugar had disappeared and none was found again until June 4th. His dietary was the same as before the treatment.

A second implantation was given on June 18th, a third on August 8th, and a fourth on September 25th. No sugar was found in the daily examination of urine from September, 1924, until February, 1925, the last day of observation of this man.

Several other cases were observed in which urinary sugar disappeared after implantation; the majority of these observations gave the impression that testicular substance influenced favorably the output of urinary sugar.

Criticism was directed to the fact that, although the urine was quantitatively tested daily, the food intake had not been measured.

The following is an example of a case in which the food was carefully weighed from September 26th, 1925, to February 28th, 1926, and the urinary sugar output measured daily.

Patient No. 41271-M.R., Jewish, entered San Quentin Prison September 10th, 1925. He gave his occupation as attorney and age as 40. His father had died at the age of 34 from cause unknown. His mother was alive and well. He had three brothers and one sister. He was married but had no children. He had had gonorrhoea in 1906 and rheumatism in 1920, lasting eighteen months. In 1923 he developed diabetes and had taken sanitarium treatment for two years for this condition. He had been able to have sugar free urine at times with proper diet.

Physical examination showed him to be normal except that his teeth were poorly preserved, poorly kept and well worn down. His blood pressure was 110/60. A Wassermann test gave negative findings. The knee jerk was sluggish but his cremasteric

and abdominal reflexes were active. He weighed 152 pounds stripped. He complained of thirst, hunger and frequent urination as well as pain in his lower lumbar region. The soles of his feet and toes had itched for the past three years. He had a tic consisting of shrugging of the shoulders when slightly excited.

A urinary test showed 1.5 per cent of sugar. He was placed in the hospital under strict observation and daily computations of the sugar was made. All of the food he took was carefully measured.

Chart 1 shows the amount in grams of fat, protein and carbohydrate he took every day for a period of approximately six months. It will be seen that before the first testicular implantation on September 8th, 1925, he was taking approximately 150 grams of carbohydrates, the same of proteins and 70 grams of fat. With this diet he was excreting approximately forty grams of sugar daily, as shown by Chart 2.

After the implantation the sugar disappeared completely from the urine except occasionally.

A second gland was given on November 13th, a third on December 7th, and a fourth on March 4th, 1926.

In the latter part of November the diet which had remained almost constant was increased until he was taking an average of over 200 grams of carbohydrate and during the Christmas holidays and subsequently his daily consumption of carbohydrates amounted to over 400 grams and occasionally as much as 1000 grams daily without the appearance of sugar in the urine.

Chart 2 shows the days on which sugar appeared together with the amount of urine excreted.

The following are the blood sugar findings:

September	27, 1925.....	140. mgm.
October	13, 1925.....	115. mgm.
October	20, 1925.....	142. mgm.
October	24, 1925.....	115. mgm.
November	2, 1925.....	120. mgm.
November	27, 1925.....	125. mgm.
January	5, 1926.....	175. mgm.
January	12, 1926.....	125. mgm.
January	17, 1926.....	115. mgm.
February	15, 1927.....	102. mgm.
February	26, 1927.....	93. mgm.
March	25, 1927.....	111. mgm.
April	8, 1927.....	123. mgm.
April	15, 1927.....	122. mgm.
April	22, 1927.....	133. mgm.
April	29, 1927.....	128. mgm.

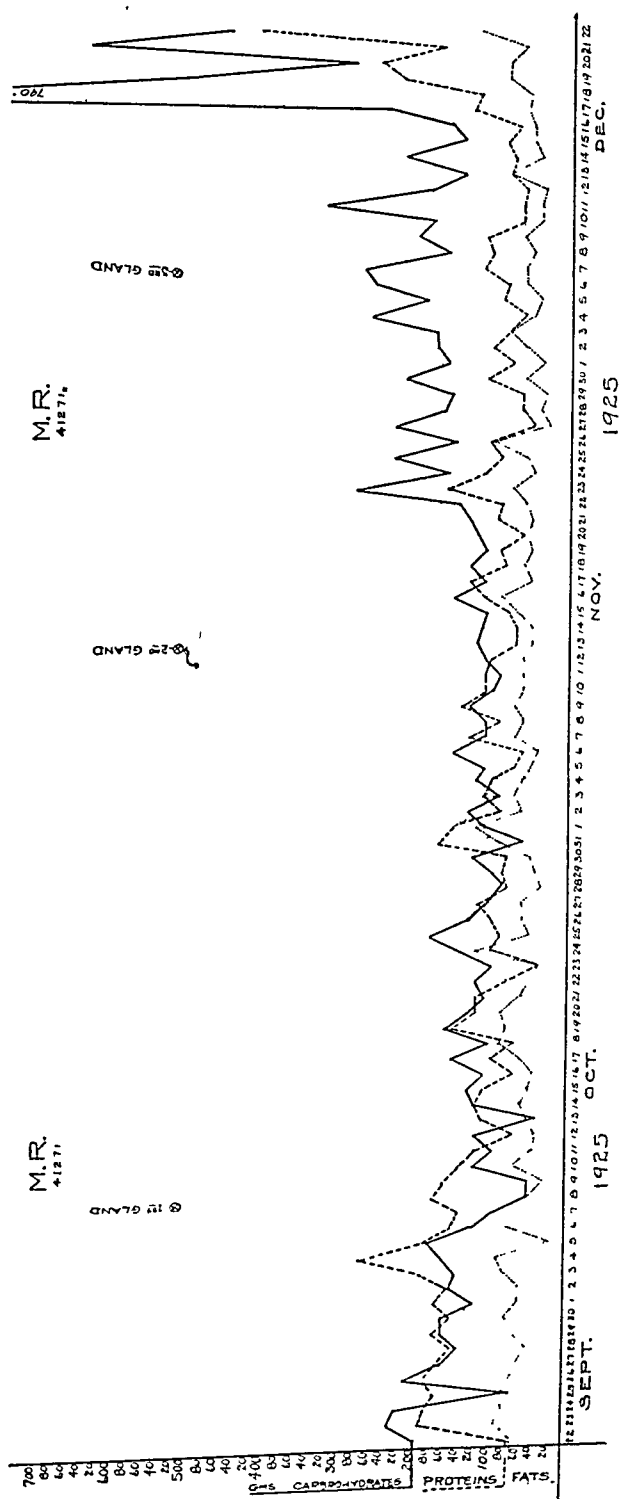


CHART I

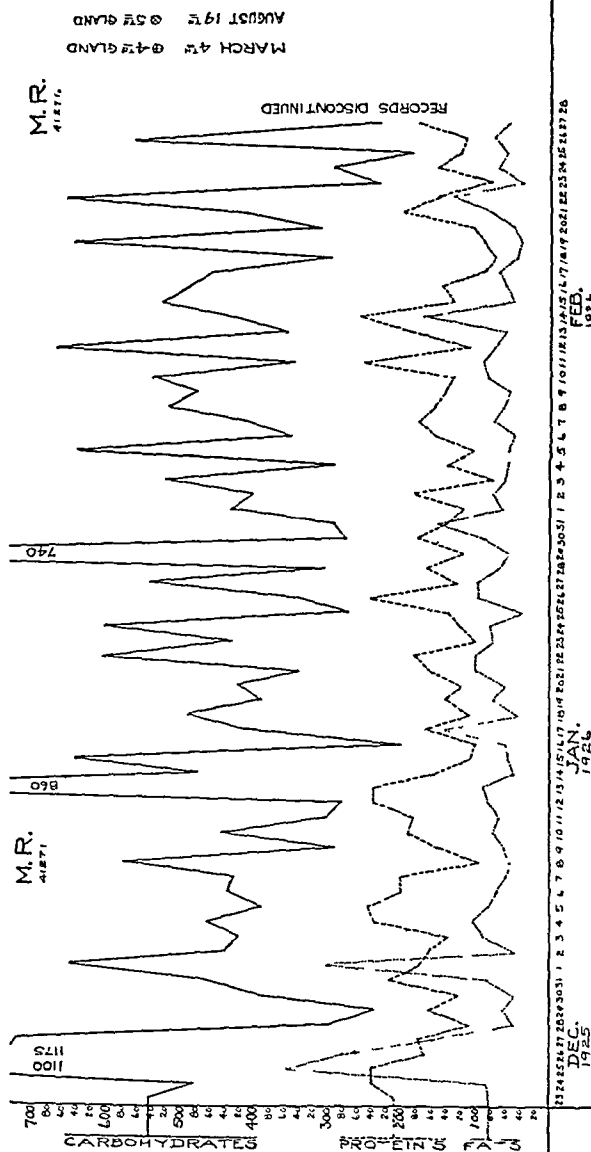
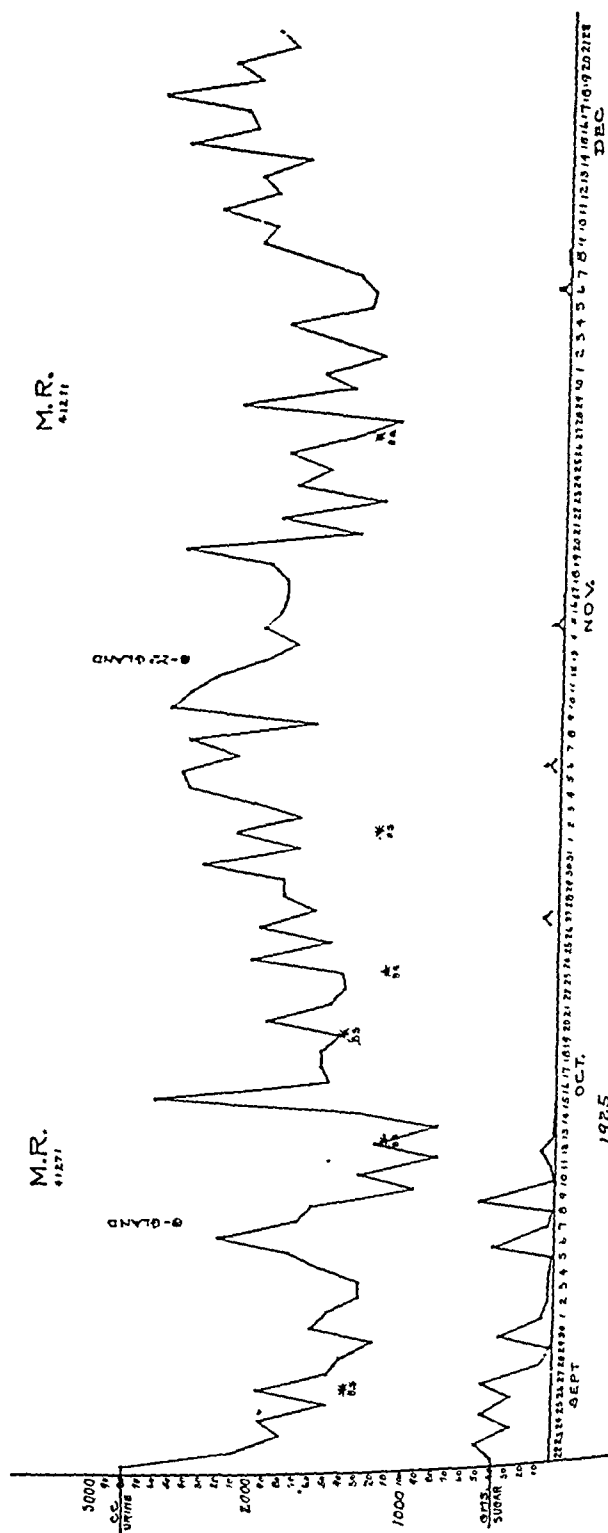


CHART I (CONTINUED)

CHART II



1925

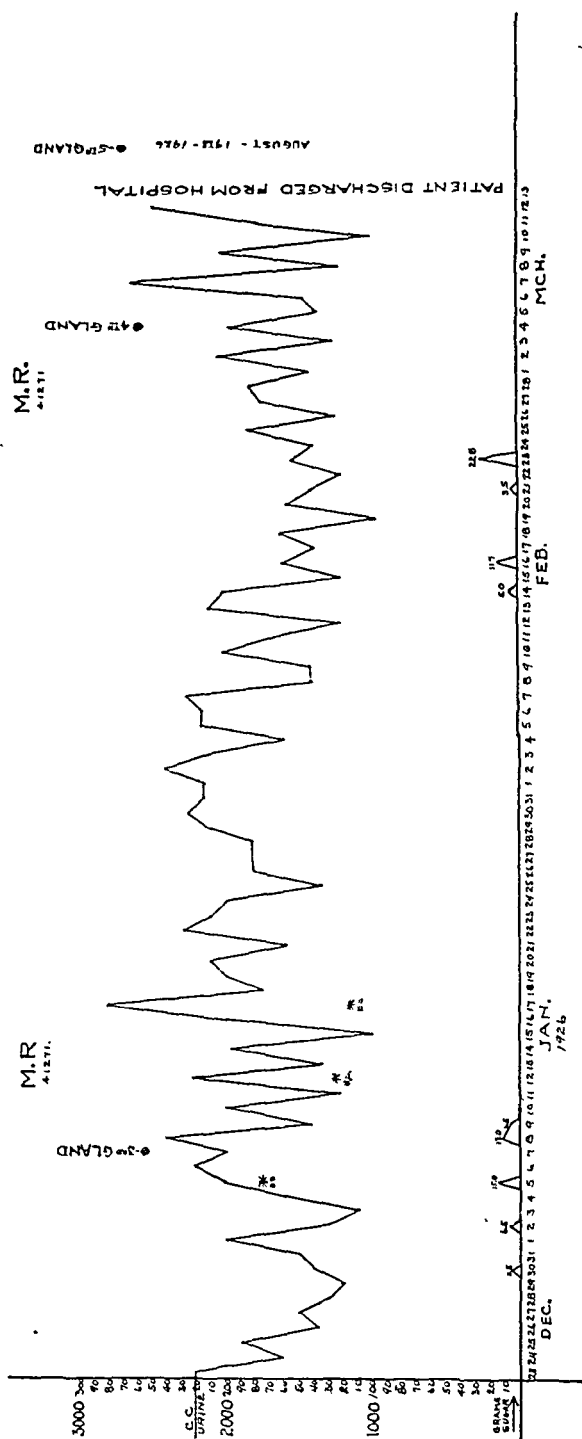


CHART II (CONTINUED)

May	6, 1927.....	125. mgm.
May	13, 1927.....	121. mgm.
May	20, 1927.....	114. mgm.
May	27, 1927.....	97. mgm.
June	10, 1927.....	93. mgm.
June	24, 1927.....	92. mgm.

The intensive study of the patient was discontinued in March, 1926. He was transferred to the prison general mess where an abundance of carbohydrate was procurable. He was given subsequent testicular substance implantations on March 4th, 1926; August 19th, 1926; February 3rd, 1927. Numerous samples of urine have been examined and at no time has sugar been found. The patient remains well and has no complaint.

These few cases seem to indicate that in some instances the output of sugar in the urine is influenced by the implantation under the skin of whole testicular substance from a lower animal.

THE INTERSTITIAL CELLS OF LEYDIG IN THE HERMAPHRODITE PIG

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OBSERVATIONS

A hermaphrodite pig, grown to maturity, weighing one hundred and eighty pounds, was reported to us by the meat inspector at the local abattoir. The general appearance of this animal resembled that of a sow, but there was one noticeable external genital malformation, namely, the ventral labial commissure, which pointed upward rather than downward. The meat was condemned because of its boarish odor. Fortunately we were able to secure the external and internal genitalia intact.

Protruding from the vulva is a clitoris, which, when unsheathed, is two inches long. It is spiral in shape and in size and configuration resembles a rudimentary penis.

The vagina and urethra are in common for two inches, the common channel beginning at the cervix uteri and ending in the urogenital orifice.

The uterus and cornua appear to be normal; the lumen is patent throughout. The right cornu seems to be continuous with the right epididymis, whereas the left horn terminates in a fallopian tube which coils around the left testis. Histological examination of the uterus reveals a normal musculature and a mucosa slightly thickened. The epithelium consists of a single layer of columnar cells. The tunica propria of the endometrium contains many glands, which are in a resting stage.

The single fallopian tube is on the left side. It is two inches in length and one-quarter of an inch in diameter.

On the antero-ventro-medial surface of the right testis is a cystic ovary which was identified by histological examination. Graafian follicles were seen in the substance of the ovarian tis-

sue. The continuity of the single ovary and right testis justifies the designation ovotestis.

The epididymes are bilaterally placed and are closely apposed to the testes as in the normal subject. The epididymis



Figure One— Photograph of ventro lateral aspect of excised genitalia of the hermaphrodite pig

consists of the characteristic tubules imbedded in a loosely woven stroma of connective tissue. The lining epithelium is of the tall, ciliated simple columnar type with elongated ovoid

nuclei and finely granular cytoplasm. At the base of the ciliated cells is an incomplete layer of basal epithelium, the arrangement forming a pseudo-stratified type of epithelium.

Accompanying each testis is a pampiniform venous plexus. The urinary bladder and ureters are normal in structure and location.

The testes are bilateral, symmetrical, intra-abdominal organs, placed at the extremities of the uterine cornua. They are normal in shape and size for an adult boar. Histologically, each testis is encased in a tunica albuginea; septa continuous with the

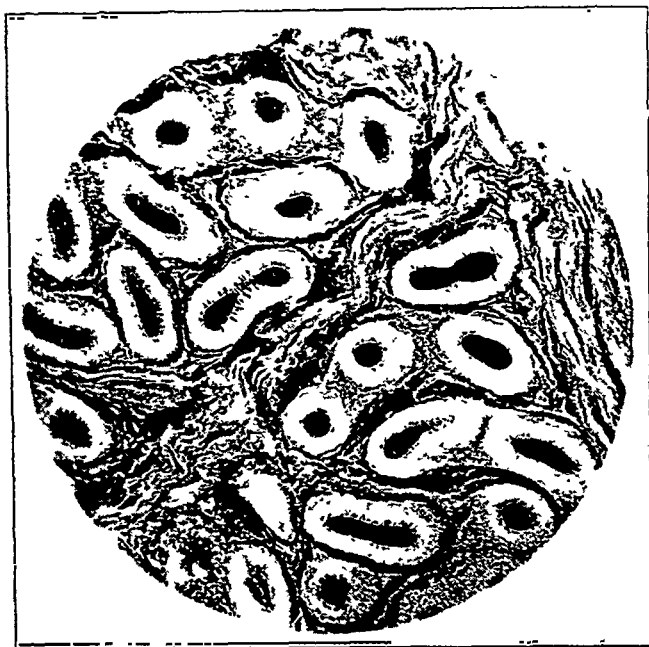


Figure Two—Microphotograph of the epididymis of the hermaphrodite pig. Low power.

capsule divide the testis into its usual multiple compartments. The testicular tubules are extremely small and atrophic, apparently having undergone functional and anatomical degeneration. The germinal cells are frequently lacking in nuclei and the cytoplasm is almost totally replaced by large fat droplets. The most striking and significant feature in the structure of each testis is the marked abundance and hypertrophy of the interstitial cells (cells of Leydig) which compose the bulk of the organ. The problem that confronts the investigator here is the significance



Figure Three—Microphotograph of the testis of the hermaphrodite pig.
Low power.

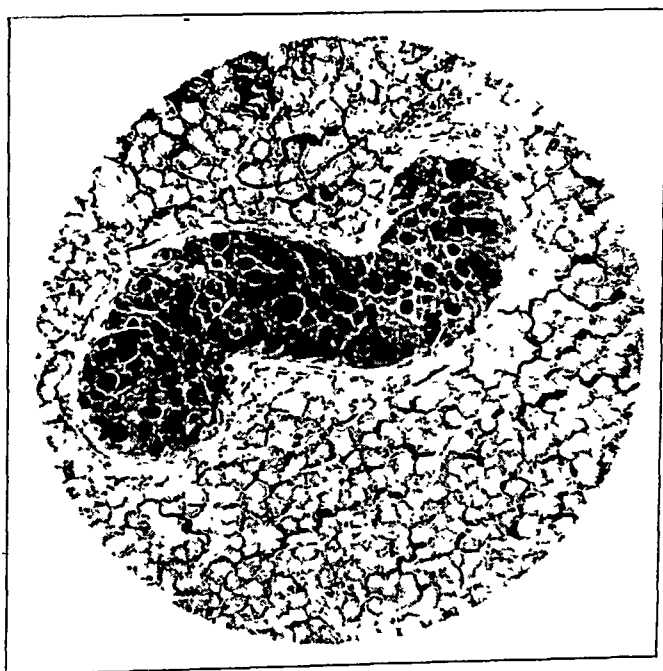


Figure Four—Microphotograph of the testis of the hermaphrodite pig.
High power.

of the preponderance of interstitial cells in the hermaphrodite testis and the reason for the asymmetry in distribution of the ovary and fallopian tube.

DISCUSSION

The gonads of the hermaphrodite pigs usually consist of an ovary or ovotestis on the left and a testes or ovotestis on the right. The ovarian patch on the testis is usually on the ventro-antero-median surface; from this fact one could assume that the corresponding part of the embryonic gonad gives rise to ovarian tissue more readily than the remainder.

Is the asymmetry of the gonads due to such factors as gynandromorphism or some difference in metabolism between the opposite sides of the body? The former hypothesis is improbable because of the frequency of the male element on the right. Bond reported a unique occurrence in a pheasant, in which each tail feather was male on one side and female on the other—a condition which can hardly be attributed to any irregularity in sex chromosome distribution. A corresponding asymmetry of the accessory reproductive organs usually accompanies the difference in the gonads. In the specimen reported here, however, the single ovotestis is on the right, whereas the single fallopian tube is on the left. Externally, the secondary female characteristics are not more pronounced on one side than the other. In some hermaphrodite animals with asymmetrical development of the gonads, the secondary sexual characteristics may be predominantly male on the right if the testis is on the right and vice versa. It is quite evident here that another factor besides hormonal stimulation is concerned, because hormones are necessarily distributed to both sides of the body. When both ovary and testis are present and functional, there is presumably a mutual counterbalance of the ovarian and testicular hormones, thereby removing the natural inhibition of either hormone when acting alone, and permitting the unknown factor to determine the asymmetry of development.

With the anlagen of both sexes present, some stimulus must foster the development of one sex with the concomitant suppression of the other, such an influence being exerted at a critical period in the evolution of the sexual elements. A retardation or delay in this stimulation or a quantitative or qualitative

change in its nature may permit the partial or complete development of both gonads with their corresponding accessory and secondary sexual structures. In four instances out of seven cases of twins, studied by Hughes, in which there were inter-embryonic vascular connections, it was found that the vascular intercommunication was followed by abnormality in sex equipment in one of the pair (2). A similar vascular phenomenon may be present in the hermaphroditic pig; witness the close apposition of the ovary to the testis.

Let us assume that the gonads are "double organs" in which the reproductive, germ cell producing elements are quite distinct, although intimately intermingled with a second gonadal constituent, an endocrine gland, called the interstitial cells of Leydig. Most writers accept the interstitial cells as responsible for the endocrine secretion. Histologically, these suggest gland cells because of their large size, abundant cytoplasm and frequent granules, which appear to be lipoidal in nature. Students of the histogenesis of the interstitial cells ascribe their origin to the hypertrophied stroma cells, the characteristic connective tissue cells of the ovary and testis, the cytoplasm of which has become increased and within which appear the distinct and peculiar granulation and lipid droplets. The hypertrophied or exaggerated size of the centrosphere is a striking feature of the interstitial cell. Probably under different conditions a reversible reaction might take place, i. e., stroma cells might be formed from interstitial cells.

Considerable circumstantial evidence indicates that there exists a reciprocal balance, a parencha-stroma interrelationship, of such a nature that a decrease in seminiferous tubules is attended by an increase in interstitial cells and vice versa. Rasmussen found in the woodchuck that the relation between the interstitial cell activity, spermatogenesis, breeding period and hibernation, indicated that in the post-reproductive period there is a marked hypertrophy of the interstitial cells accompanying a corresponding decrease in size of the seminiferous tubules with a suspension of spermatogenesis.

Cryptorchidism, congenital or experimental, exhibits an increase in interstitial cells. Experiments on guinea pigs have been carried out by various investigators, and especially Moore, wherein the testes were confined to the abdominal cavity with

the blood supply, nervous connections and vasa deferentia intact. In consequence, there resulted a slow but complete disorganization of the germinal epithelium of the seminiferous tubules. The germinal cells became unattached and escaped into the lumen of the tubules. Later there was a decrease in size of the tubules and an increase in the interstitial cell mass. The cause of the testicular degeneration in these cases was probably the higher temperature within the peritoneal cavity. The same cause would operate in the testis of the hermaphrodite pig, because both of these intra-abdominal organs exhibited the atrophy of the general elements and the increase in interstitial cells. A condition very similar to the cases of cryptorchidism and hermaphroditic testis can be brought about by applying heat to the testis over a long period of time or at frequent intervals (6). Moore ascribes a heat regulating function to the scrotum. This scrotal function is found to be necessary not only for the testis to produce mature germ cells, but even to retain those previously differentiated.

Occlusion of the vas deferens in the rabbit does not lead primarily to degeneration of the germinal epithelium up to six months, but does cause the epididymis to increase to three to four times its normal size (5). This enlargement of the epididymis causes an upward displacement of the testis into the inguinal canal; this location is the most probable explanation for the interstitial cell hypertrophy and degeneration of the tubular epithelium. The interstitial cell seems to express an alteration in growth and metabolic balance between parenchyma and stroma.

The interstitial cells are relatively larger and more abundant in the testes of tuberculous patients in whom there is considerable degeneration and a general infantile condition of the seminal epithelium.

Kingsbury's careful studies of the interstitial cells of the ovary of the cat (elements presumably homologous to the interstitial cells of the testis) strongly support the theory of the function of these cells as absorbers of degenerating and disintegrating material (7). In the ovary many of the oöcytes disintegrate. In the immediate vicinity of such oöcytes and their follicles the interstitial cells contain much lipoid debris. Their presence is transitory and their number proportional to the

abundance of degenerating follicles. This observation might suffice to explain in part the abundance of interstitial cells in the testes of cryptorchid animals, in the testes of woodchuck during the hibernating phase of the cycle of reproduction, in the testes kept at too high a temperature for too long a time, and, to some degree, in the testes of the hermaphrodite pig.

We wish to express our appreciation to Dr. Henry Knowler, Professor of Anatomy in the University of Alabama, and to Dr. Edgar Beckham, veterinary surgeon, for the assistance they rendered in the study of this specimen.

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THE EFFECT OF THYROID EXTRACT UPON BODILY FUNCTION IN HYPOTHYROIDISM

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From the Endocrine Clinic Evans Memorial
Evans Publication No. A-84, 145

BOSTON

The administration of thyroid extract to patients with hypothyroidism has given such generally satisfactory results that the need for clinical studies of its effects on individual organs and their functions has not, until recently, been apparent. The response of the myxedemic to adequate medication was usually so satisfactory that "no questions were asked." With improved methods of diagnosis, however, an increasing variety of symptoms has become associated with thyroid hypofunction, and knowledge of the effect of thyroid extract upon individual functions has become extremely important.

This paper represents an attempt to contribute to that knowledge by means of laboratory and clinical studies of a series of twenty-five patients with definite thyroid failure who have been under treatment during periods of time sufficient for repeated observation of the changes in organic function which occurred as the thyroid lack was compensated. The effects studied were those upon weight, nitrogen metabolism, pulse rate, blood pressure, and cardiac function, together with basal metabolism.

An analysis of the changes of basal rate in the entire group of patients fails to show any exact relation between the initial magnitude of its depression and the amount of thyroid extract required to raise it to normal. Thus, in one patient with an initial reading of -34% the basal rate normalized promptly with a dosage of three grains daily, while in another, with an initial rate of -14% , eight grains a day were required to raise the metabolic rate to normal. In the entire series, the dosage has shown an individual variation of four hundred per cent.

The reasons for this discrepancy are not clear. Every patient in this series received the same preparation of thyroid extract, so that the differences in dosage cannot be explained

on the basis of varying content of thyroid substance. Variations in absorption from the digestive tract may be a factor, but hardly the entire cause of these differences. Neither could they be explained by such factors as weight, sex, age, or the presence or absence of myxedema. The subject is too complex for discussion in a paper of this nature, but from the clinical point of view it is worth while emphasizing the fact that the amount of thyroid extract which will be required to normalize the basal metabolic rate cannot be accurately calculated from the magnitude of its initial depression. Several patients in this series developed mild symptoms of overdosage before the basal metabolic rate had reached normal. Therefore the initial dose must be small enough to be safe, and should be increased only when successive determinations of the metabolic rate show unsatisfactory response to the amount which is being administered.

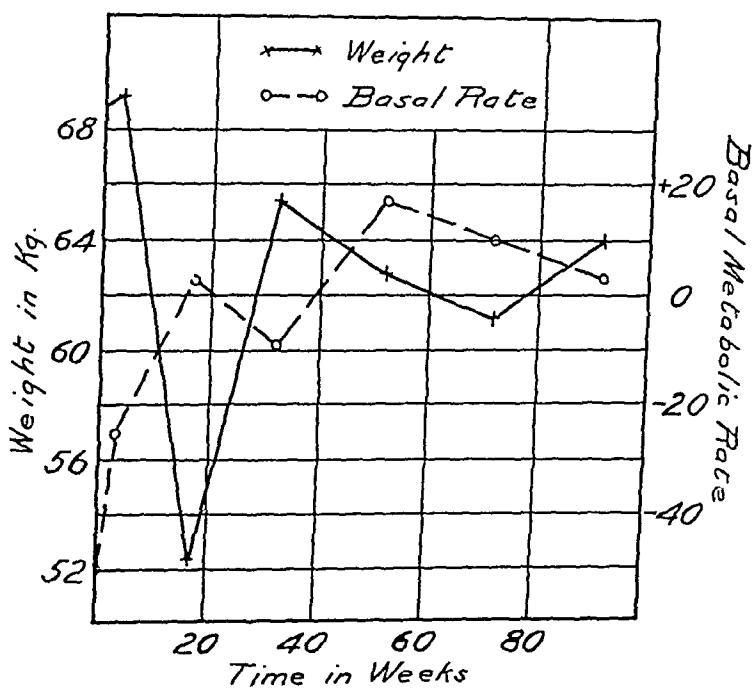


Chart 1. Showing variations in weight and basal metabolism in a myxedemic over a period of 90 weeks. The dosage of thyroid was constant during that period.

In the majority of the patients in this series it was necessary to diminish the dosage slightly when the basal rate reached normal. It apparently requires less thyroid extract to main-

tain normal metabolism than is necessary to raise it to that level when it is depressed by thyroid failure. This conclusion is in accord with the findings of Sturgis and Whiting (1).

Because of its effect upon basal metabolism, and because myxedemic patients often show a striking initial weight loss under treatment, there exists a general impression that thyroid extract possesses a specific weight reducing property, even in patients whose overweight is not coexistent with hypothyroidism. The observations here reported do not support this theory. Those patients in the series who were myxedemic showed a marked initial loss of weight as the myxedematous deposits disappeared, but in every case this initial loss was followed by a gain in weight, with the result that, as the basal metabolic

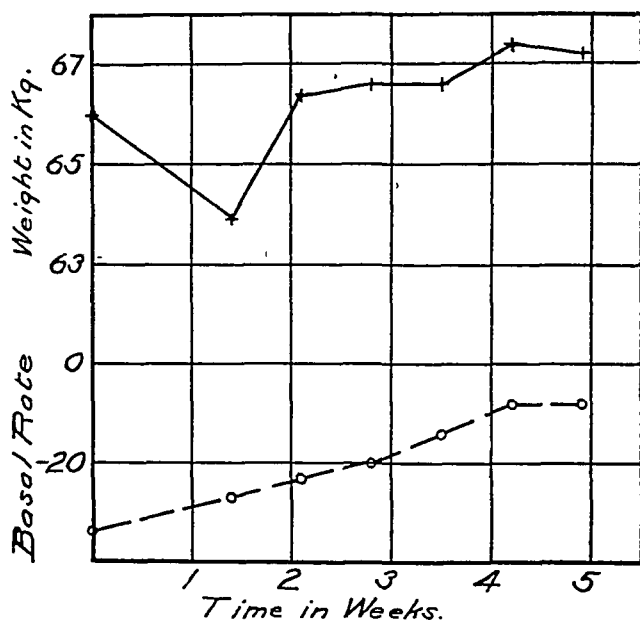


Chart 2. Showing weekly variations in basal metabolism and weight in a patient with thyroid failure but without demonstrable myxedema. The initial weight loss is much less in the myxedemic, and is followed by definite and permanent gain. The dose of thyroid extract was constant during the period charted.

rate reached normal, the weight also closely approximated the normal value for the individual according to the West and Dreyer Standards. This effect is illustrated in Chart 1.

Those patients who did not have myxedema which could be demonstrated clinically showed only slight initial losses of weight under treatment. This slight loss is apparently due to

increased elimination of water from the body, since in practically every case it was accompanied by increased urinary output. In all the non-myxedemic cases in this series, the slight initial weight loss was followed by a gain in weight so that by the time the basal rate had reached normal, the patients weighed more than at the beginning of treatment. The changes in weight and basal metabolic rate in a case characteristic of this group are shown in Chart 2.

The results obtained in this series offer no evidence in support of the idea that thyroid extract, in doses adequate to maintain the basal metabolism at a normal level, has any specific weight reducing property. Only when the dose was large enough to raise the metabolic rate above the upper limits of normal was there any progressive and maintained reduction of weight in the cases under consideration. The weight changes observed indicate that thyroid extract will dissipate myxedematous deposits, and will overcome a tendency to fluid retention as it normalizes the metabolism of the patient with thyroid

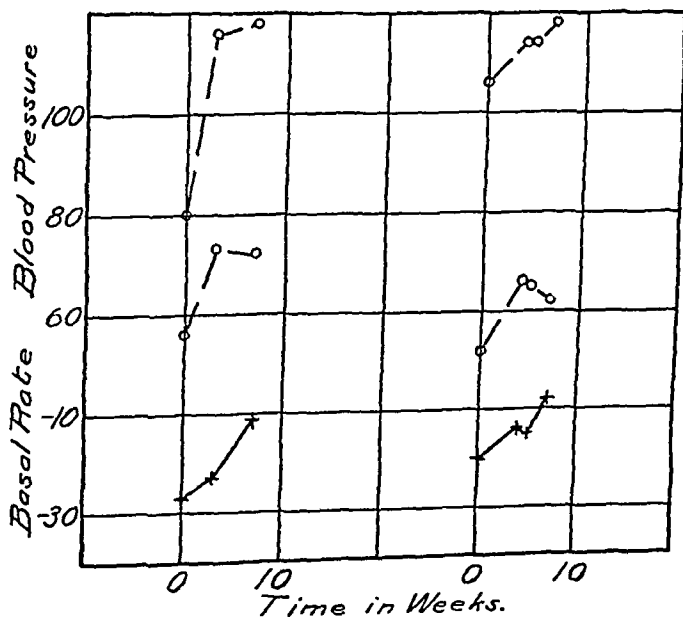


Chart 3. Characteristic changes in blood pressure and basal metabolism in two patients with thyroid failure under thyroid medication. The pressures rose to practically normal values as the basal metabolism became normal.

hypofunction, but they give no support to its use in the treatment of obesity not associated with that condition, and strongly suggest that when it does cause reduction of weight in non-

thyroid obesity, it does so by producing a toxic, not a physiologic effect.

The effect of thyroid medication on blood pressure as observed in this group of patients does not indicate that it has any specific directional influence upon arterial tension. In twenty cases there was definite hypotension, and in all of these the blood pressure showed higher values, when the basal metabolism had reached normal, than those initially observed. Examples of the changes observed in this group are shown in Chart 3.

In three cases definite hypertension was present. In two of these, significant reduction in blood pressure coincided with the production of normal basal metabolism with thyroid extract; in one there was no change in the pressure. Chart 4 illustrates the changes in blood pressure and basal metabolic rate in a patient with initial hypertension.

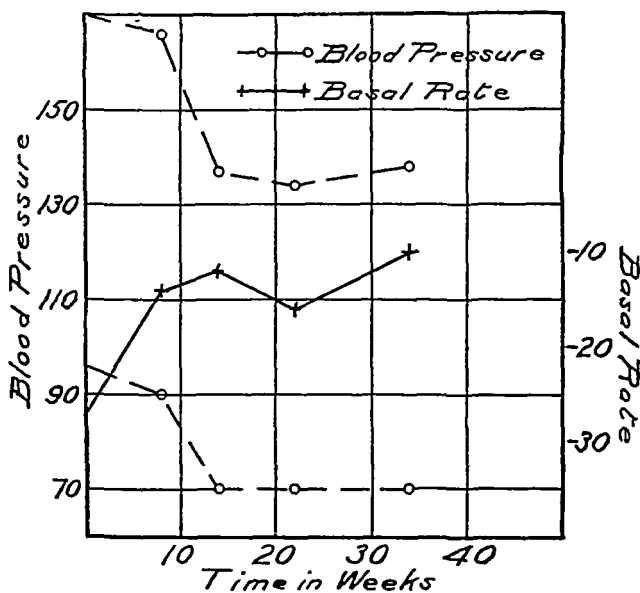


Chart 4. Showing fall in blood pressure to normal as the basal metabolic rate was normalized by thyroid extract. The patient showed no demonstrable myxedema.

Two patients showed normal blood pressure. No significant change occurred as the result of thyroid administration. It appears, therefore, that in the presence of thyroid failure thyroid extract in proper dosage has no specific directional

effect upon blood pressure, but that under its influence upon nutrition in general, in the absence of organic vascular disease, arterial tension tends to return to normal.

Another effect of thyroid extract studied in this series of patients was that upon the blood chemistry. It has long been agreed that nitrogen metabolism is disturbed in patients with subnormal thyroid function, but the effect of thyroid medication on the nitrogen retention in the blood has not been thoroughly studied. From the observations in the series here reported, it appears that this retention tends to disappear as the basal metabolism is normalized, except in those patients in whom arteriosclerosis involving the kidneys is present. Table 1 shows the characteristic changes in the blood chemistry in two patients under thyroid medication. It will be seen that as the basal metabolic rates reached normal the blood nitrogen values also fell to normal.

BLOOD CHEMICAL CHANGES

<i>Case</i>	<i>N.P.N.</i>	<i>Urea N.</i>	<i>Uric Acid</i>	<i>Basal Rate</i>
1	45	16	6.5	—34%
	30	10	3.5	—22%
2	42	17	3.5	—30%
	30	15	3.5	+26%

From our observations, no relation between nitrogen retention and blood pressure level in hypothyroidism can be established. The results tabulated in Table 1 were obtained in patients both of whom had initial hypotension which rose to practically normal levels as the nitrogen retention in the blood was eliminated. The change in blood pressure is not the direct result of the changes in blood chemistry; both are evidences of the normalization of body function by thyroid medication. From the clinical standpoint, neither abnormally high nor abnormally low blood pressure is a contraindication to such medication in thyroid failure. Either high or low pressure may be expected to approximate normal under its influence if no organic vascular disease is present.

More important than its effect upon blood pressure and blood chemistry is the effect of thyroid extract upon the heart. It is generally believed that thyroid failure produces bradycardia and that thyroid extract possesses a specific acceleratory

effect upon the pulse rate proportionate to its effect upon the metabolic rate. A study of Chart 5 shows that while these relations of pulse to metabolic rate are true in the main, a large number of exceptions to the rule are encountered. For example, one patient with a basal metabolic rate of -49% had a pulse rate of 71 per minute, while in another with a basal rate of $+26\%$ the pulse rate was 72 per minute. In neither patient was any cardiac disease demonstrable.

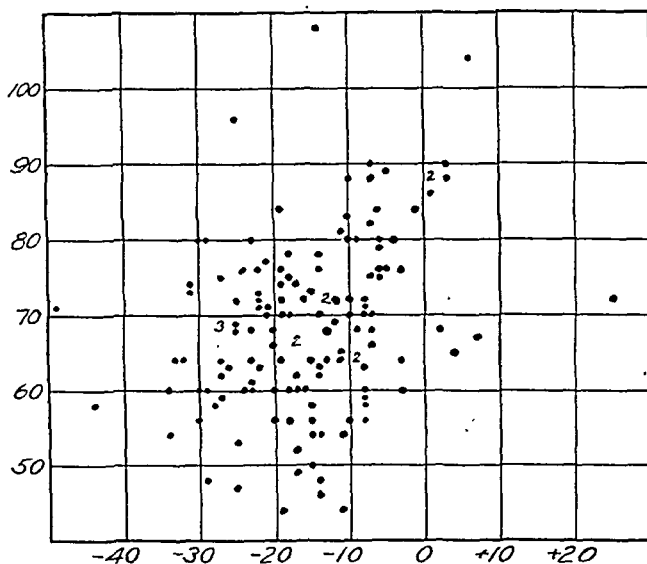


Chart 5. Showing the relation of pulse rate and basal metabolic rate in 141 observations. Pulse rate is the average determined during estimation of basal metabolism. The metabolic rates are plotted on the ordinates, the pulse rates on the abscissae.

No convincing explanation of these variations from the general rule exists, and a discussion of theories would not be profitable. Studies with the electrocardiograph are being carried on in our clinic with the purpose of answering this, among other questions, and a detailed report will appear later. At present it is sufficient to emphasize the fact that a normal or accelerated pulse rate does not preclude a coexisting hypometabolism due to thyroid failure. The pulse rate is fully as dependent upon the condition of the heart itself as upon the metabolic rate, and there is a convincing amount of evidence that cardiac function is often seriously disturbed by thyroid insufficiency (2, 3, 4, 5), though Fahr's observations on "myxedema heart" have not been confirmed by other observers (4, 6).

In this series, five patients showed definite evidence of disturbed cardiac function. In three, it consisted of frequent premature beats and dyspnoea on mild exertion; in two, pain, anginal in character, produced by slight exertion; in one, attacks of paroxysmal tachycardia. Contrary to the general ideas upon this subject, the cardiac condition of all these patients was benefited by thyroid medication.

In order to explain the effect of thyroid extract on the heart in hypothyroidism, a brief consideration of the effect of thyroid failure upon that organ is necessary. Means (3) has shown that in myxedema the cardiac output per systole may be reduced to 50 per cent of the normal. Thacher and White (2) report that with the electrocardiograph the myxedemic heart shows the same changes that characterize the findings in myocardial exhaustion. Whether myxedema be present or absent, thorough examination of the heart in hypothyroidism elicits signs and symptoms of impaired cardiac efficiency in the majority of instances, without bringing to light evidence of organic heart disease. Moreover, in the absence of organic disease such signs and symptoms either disappear entirely or are greatly benefited after bodily metabolism and nutrition have been maintained at the normal level for a period of weeks or months by the proper amount of thyroid extract. In short, the evidence is convincing that in the majority of instances, symptoms of abnormal cardiac function in hypothyroidism are due to disturbed nutrition or nervous control, or both, and are secondary to the thyroid failure and not to organic heart disease, except in a small minority of patients. Since, however, the interference with cardiac function may be as severe in the former as the latter, care must be exercised in giving thyroid extract to the patient with evidences of deranged cardiac function, for serious or even fatal results have followed its administration under such conditions (7).

A study of the effect of thyroid extract on the cardiac function of the patients in the series here reported shows that as a rule the pulse is accelerated and the blood pressure raised *pari passu* with the basal metabolic rate, but that the heart's response to increased demand is not greatly increased until general nutrition has been maintained at normal for a period of weeks or months. In other words, administration of thyroid

extract causes an increase in both the work done by the heart and in its nutrition, but the former begins earlier and for a time increases faster than the latter. If due allowance is not made for this sudden increase in work, the symptoms of cardiac insufficiency may be greatly increased, but if the general activity of the patient is curtailed during the period required for the normalization of general and cardiac nutrition, marked diminution or entire disappearance of the symptoms results, provided, of course, organic damage be absent.

One of our patients found that her premature beats and sense of faintness were markedly increased by even small doses of thyroid extract if she carried on her usual activities, so that it was impossible to give enough to normalize her basal metabolism without producing a disturbing aggravation of her symptoms of cardiac insufficiency. When, however, she was put to bed, it was possible to increase the dosage to an amount which rapidly brought her basal metabolic rate to normal without producing any increase in cardiac symptoms. After the metabolism and general nutrition had remained normal for three weeks, gradual return to her usual activities, without change in the dosage of thyroid extract, caused no increase in the cardiac symptoms. For the past six months they have been entirely absent, and repeated examinations have failed to detect any abnormality of cardiac rhythm. Similarly, in the patients with anginal pain, a sharp curtailment of activity was necessary during the period of adjustment to normal bodily nutrition and energy elaboration, but normal conditions once established, gradual return to accustomed activities was not accompanied by return of symptoms.

From the evidence at hand, it seems clear that thyroid extract has two rather distinct effects upon the heart in hypothyroidism. One is the increase in work produced by the medication. This, as evidenced by the changes in pulse rate and blood pressure, takes place before the second effect—improvement in nutrition—has been realized, and time is required for the benefit to nutrition to become sufficient to compensate for the increase in work done. On this basis, the apparently paradoxical effects of thyroid extract become logical, and the necessity for absolute control of the patient with severe cardiac symptoms during its administration becomes evident.

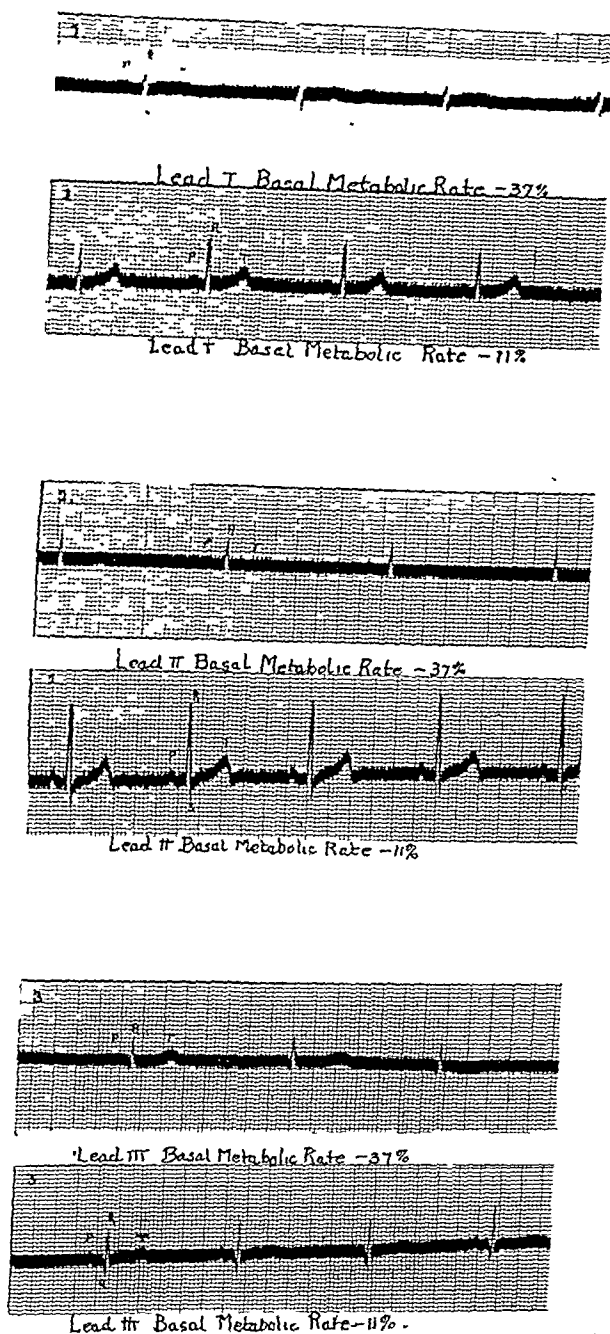


Chart 6 Showing the changes in the electrocardiographic tracings occurring in a myxedemic patient under thyroid medication. The pulse rate showed no significant change during the period of observation. (See Chart 9.)

Such control consists in a complete and careful examination of the patient's cardiovascular system before thyroid medication is begun; in the use of small initial dosage; in adequate curtailment of the patient's activities; and in frequent examinations of the patient, supplemented, when possible, by determinations of the basal metabolic rate as often as they seem likely to show significant changes. Repeated electrocardiographic studies are not as a rule essential, but may furnish valuable evidence concerning the level of cardiac function. Changes in the records are often well marked before pulse rate or the usual methods of examination show any characteristic effect of the medication (Chart 6).

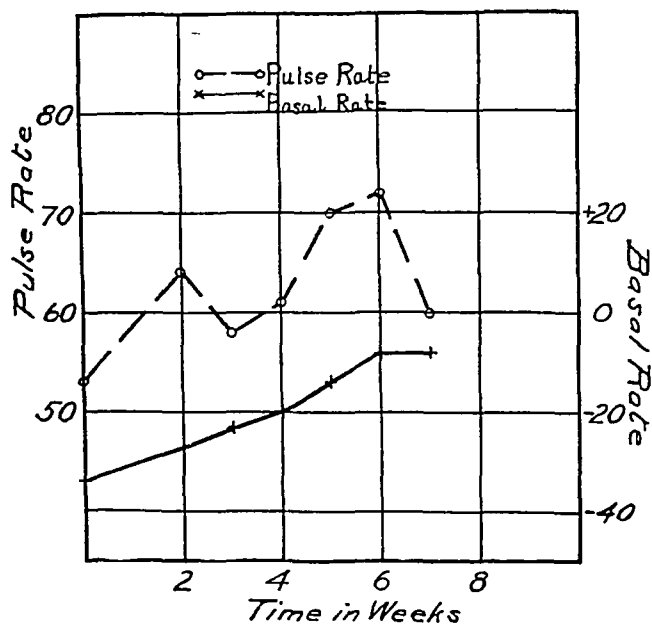


Chart 7. Showing typical acceleration of pulse rate as basal metabolism rises to normal in a patient with hypothyroidism under thyroid medication.

The pulse rate, especially in patients with cardiac disturbances, is not in our experience a reliable index of changes in the basal metabolic rate during the period in which it is rising to normal. While changes in the pulse rate usually parallel those in the basal metabolic rate, there are too many exceptions to this rule, even though the heart is organically sound, to justify confidence in the pulse rate as a reliable guide to changes in metabolism until repeated observations have made

clear the relation of the two in each individual patient. Chart 7 shows the characteristic parallelism between pulse rate and basal metabolic rate during thyroid medication; Chart 8 shows inversion of the usual pulse reaction; and Chart 9, the failure of the pulse rate to give any indication of considerable changes in basal metabolic rate.

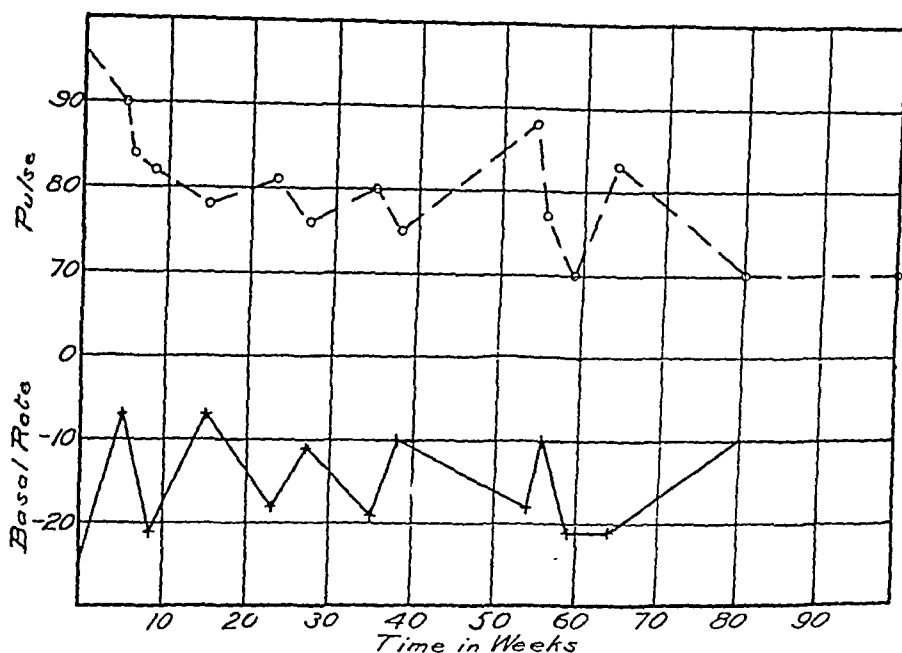


Chart 8. Showing fall of pulse rate to normal as basal metabolic rate rises to normal in a patient with hypothyroidism under thyroid medication.

SUMMARY

In conclusion, the following facts seem established from the study of the cases here reported:

1. Thyroid extract in non-toxic amounts has no specific action in reducing body weight, except as it dissipates myxedemic deposits and causes the elimination of abnormal accumulations of fluid. By its effect on nutrition it frequently causes a gain in weight as basal metabolism becomes normal. Progressive loss of body weight as a result of its administration is, as a rule, a toxic effect. Its use as an aid in reducing weight in patients with normal thyroid function is therefore illogical, and either inefficient or dangerous.

2. Its effect upon blood pressure in hypothyroidism indicates that it has no specific directional influence on vascular ten-

sion, but that through its influence upon nutrition it tends to bring either high or low blood pressure back to normal unless prevented by the presence of organic vascular disease.

3. Nitrogen retention, as evidenced by increased values for the nitrogen fractions in the blood, is corrected by thyroid extract in therapeutic doses when the retention is due to thyroid failure.

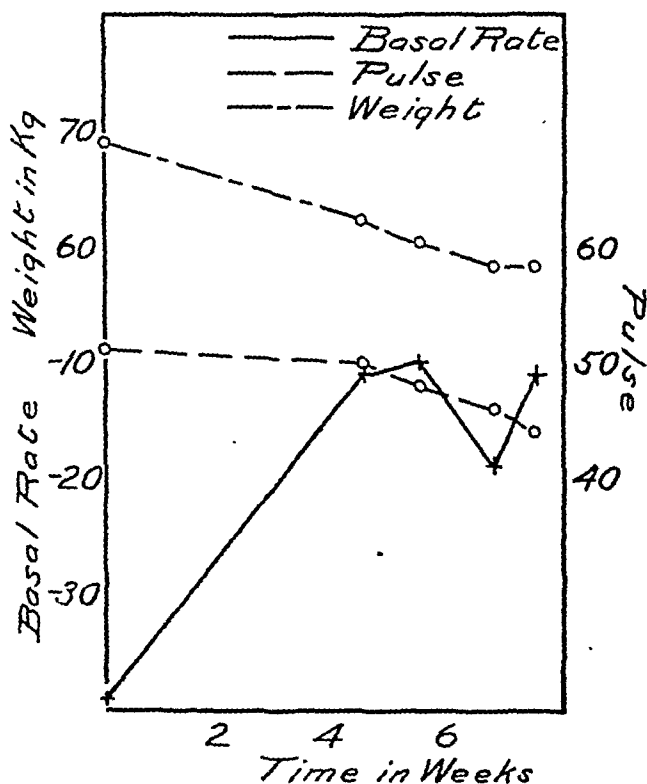


Chart 3. Showing little change in pulse rate while the basal rate rises to normal in a patient with hypothyroidism under thyroid medication.

4. The relation between depression of basal metabolic rate and pulse rate is not constant. While bradycardia generally accompanies depression of the basal metabolic rate due to thyroid failure, there is a significantly large number of exceptions to this rule.

5. Changes in pulse rate are not reliable criteria of changes in basal metabolic rate in patients with hypothyroid-

ism until the individual relation between them has been determined.

6. In therapeutic doses, thyroid extract in hypothyroidism has two effects upon the heart. It increases its work promptly and rapidly, and improves its nutrition slowly. Therefore, signs of cardiac insufficiency do not contraindicate its administration but do emphasize the need for care in its use and adequate curtailment of the patient's activity during the period of readjustment of metabolism.

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FURTHER STUDIES ON TESTICULAR GRAFTING

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For the past three years several members of the Physiology Department of this University have been engaged in a study of the influence of endocrine factors on spontaneous activity. Rats have been used as the experimental animals. The activity has been recorded by means of revolving cages substantially as described by Stewart (1) some thirty years ago. A few modifications in the cages have been made as described by Durrant (2). Among the most clean-cut results secured was the marked depression of activity following castration (3).

Numerous attempts have been made by means of grafting and injections of various testicular extracts to ameliorate the lethargy (4). With one or two suggestive exceptions the results have been completely negative. Smith (5) has recently reported that the effects of hypophysis extirpation can be corrected by daily administration of fresh grafts of this organ. It was hoped that the same method might be utilized in case of testicular deficiency to restore, at least in some degree, the activity of the animal. In the studies herein reported seven senile male white rats and eight castrated rats four or five months old were used. Material for the grafts was obtained from vigorous young male rats weighing about 130 grams each. At this stage of development activity is near its maximum and hence the glands are presumably at the height of their hormone production. The material was taken from the donors with aseptic technic. The tunica vaginalis was removed together with a long coiled artery that permeates the tissue beneath the tunica. The soft pulpy mass was then placed in a sterile recording syringe from which it was ejected, following the Stanley method (6), into the recipient. The grafts were placed successively in four different sites under the skin of the belly and within

the scrotum on the two sides. At first 0.2 cc. was implanted in each animal three times a week. This proving inefficacious, 0.1 cc. was used each day for two weeks. Again after securing negative results, for the next week the daily dosage was increased to 0.2 cc. The following week the dosage was increased to 0.4 cc. Needless to say, antiseptic technic in making the injections was followed throughout. In accordance with the experience of most other observers the material injected soon became necrotic but was resorbed in practically all cases without any discharge to the surface.

With one exception the activity of the animals was not perceptibly affected either during the period of the grafting or for two weeks afterward. In one remarkable instance, however, a senile animal that was averaging only about 200 revolutions a day for ten days preceding the experiment and throughout the course of it began on the fifth day after the reception of the last graft to show a remarkable increase in activity. For the next week the daily revolutions were: 7000, 6000, 2700, 5200, 9200, 44,600 and 29,000, respectively. On the eighth day the animal died after having made only 500 revolutions. In the study of hundreds of animals under various conditions only one other case at all comparable to this has been seen. This was a female which for a brief period showed a somewhat similar degree of excessive activity. Both cases might perhaps not unfairly be characterized as acute mania. In case of the female no cause for the phenomenon could be determined. In view of the paucity of the data, speculation as to the reason for the remarkable result in the case of the male just referred to would be unprofitable. The finding, however, would seem to justify a further extension of the grafting experiments.

Although the outcome of the experiments as regards the main point at issue was disappointing, a few collateral observations were made which indicate that the grafts were not entirely without effect. As is well known, the hair coat of senile rats becomes coarse and scrawny and often acquires a brownish discoloration. In the senile animals involved in this study a quite obvious improvement of the hair coat was noted. The hair became finer and the discolored hairs, to a considerable extent, were displaced by a fine silky white growth. At the end of the investigation the experimental animals were placed with their

controls in housing cages. In general the animals that had received the grafts gave the impression of being more alert and vivacious than their controls.

SUMMARY

The activity of eight castrated young male albino rats and of seven senile males was determined by the revolving cage method. For a period of five weeks the animals received repeated implantations of fresh rat testicle material. One senile animal showed a remarkable augmentation of activity five days after the last implantation. The other animals showed no significant increase. The hair coat of the senile group became softer and whiter. Both groups when returned to the housing cages seemed more alert than their controls.

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FURTHER OBSERVATIONS ON THE DEPRESSOR SUBSTANCE IN LIVER EXTRACT*

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Because of the very unpleasant notoriety that has come to the writer through the sensational reports of the daily press, it seems desirable to make it clear that his interest in the depressor action of liver extract is primarily physiological. As far as the clinical use of liver extract for the relief of hypertension is concerned, it is in the hands of Macdonald and others, and the problem of the writer has been to ascertain, if possible, whether the depressor effect is due entirely to histamine (and cholin), or whether there is an autocoid secreted by the liver which is responsible in part, at least, for the lowering of blood pressure. The statement that histamine is a new substance discovered by the writer is absurd, and was never made by him. In a previous communication (1926) some evidence was given for concluding that there is no depressor autocoid secreted by the liver, unless, indeed, histamine (and cholin) be so regarded. The present paper is the result of an attempt to apply the method used by Sharpey-Shafer and Macdonald (1926) to separate the depressor substance of the pituitary from the pressor substance, in a further effort to discover a specific secretion.

Fresh liver was put through a meat grinder, spread on glass plates and dried at 60°-70° C. It was kept in a dessicator over sulphuric acid until needed. Weighed amounts were ground to a fine powder and extracted with absolute alcohol in a Soxhlet's apparatus for twelve hours. The alcohol was evaporated, leaving a fatty mass of dark brown color. The liver residue after extraction in the Soxhlet apparatus was again extracted with isotonic Ringer's solution, in concentrations varying from 10 per cent to 20 per cent in different experiments. These extracts were filtered and treated with ferric oxide to remove the proteins. These solutions will be referred to as solution "A." The

*The expenses of this research were met by a grant from the Board of Research of the University of California.

alcoholic extracts were made up in 10 per cent solutions with hot Ringer's and the fat filtered off. These are solution "B." In addition, liver was extracted with petroleum ether, then with absolute alcohol, and the same procedure as above followed. The petroleum ether fraction in 10 per cent solution is solution "C."

Dogs were used in most cases. The blood pressure was taken from the left carotid artery, and the injections were made into the internal jugular of the right side. The following protocols are illustrative:

December 29, 1926. Dog, 13 kgm. Under morphin and ether anesthesia the initial blood pressure was 144 mm. Hg. After intravenous injection of 5 cc. solution "B," blood pressure fell to 102 mm.; after solution "B," 10 cc., blood pressure fell to 94 cc. Solution "A" proved inert in all quantities.

January 21, 1927. Dog, 20 kgm. Under morphin and ether anesthesia the initial blood pressure was 130 mm. Hg. Under intravenous injection of 1 cc. solution "B" (extracted with ether instead of absolute alcohol), blood pressure fell to 94 mm.; after solution "B" as above. 3 cc., pressure fell to 70. As a control 0.1 mgm. histamine caused blood pressure to fall to 70 mm. Solution "A" was inert in all quantities.

January 29, 1927. Dog, 10 kgm. Under morphin and ether anesthesia the initial blood pressure was 150 mm. Hg. After intravenous injection of 1 cc. solution "B," blood pressure fell to 134 mm.; after solution "B," 3 cc., pressure fell to 110 mm. Solution "C" proved inert in all quantities, as did solution "A."

These experiments have been repeated many times, using fresh liver as well as dried, and the results have been the same in all cases. It is obvious, therefore, that this method fails to reveal a specific autocoid having a depressor action on the circulation, admitting, of course, that such an autocoid might be soluble in absolute alcohol.

To recapitulate, the blood pressure curves after the injection of liver extract are identical with those after the injection of histamine (and cholin) in the dog. The skin reaction of liver extract is the same as that of histamine, the wheals being indistinguishable. The reaction of smooth muscle to liver and to histamine is the same. Direct observation of the capillaries of the cat's ear shows the same reaction to liver extract as to histamine. The effects of liver extract and of histamine on the heart are similar. Chemical analysis shows the presence of histamine and cholin.

On the other hand, the clinical observations of Macdonald (1926) and others, show a more prolonged fall of blood pressure after the injection of histamine, or histamine and cholin, and

this has led to a lurking suspicion that there is some other depressor substance in the liver extract, than histamine (and cholin). Physiologically it would seem superfluous for the liver or any other organ to secrete a hormone for regulating the blood pressure, when there is already present a delicate nervous and physical mechanism for its regulation. May it not be that the process of manufacture has in some way altered the histamine (and cholin) in such a way as to make its effects more lasting, and that we are in reality dealing with a pharmaceutical preparation rather than with a substance per se elaborated by the liver? In view of all the facts this would seem to be a logical explanation, and it in no way detracts from the usefulness of liver extract in the treatment of essential hypertension. That usefulness is being weighed in the balance by the clinicians, and so far it seems not to be wanting in suitable cases.

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BLOOD SUGAR CURVES IN DIABETES INSIPIDUS AND IN HABITUAL AND EXPERIMENTAL EXCESSIVE WATER DRINKING

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On the basis of Engelbach's (1) conclusions that hypopituitarism suggests an increased carbohydrate tolerance, John (2) has diagnosed from the blood sugar curve test a co-existing diabetes mellitus or prediabetic state in five women with clinical pituitary dystrophy; characteristic findings were a high renal threshold for glucose. However, Howard (3) has postulated "a decreased sugar tolerance in pituitary disease except in the later stages when the pars intermedia has been destroyed by pressure or invasion when increased sugar tolerance is to be expected." Janney and Henderson (4) and more recently Major (5) regard an abnormal sugar tolerance curve solely as an indication of endocrine disturbance. Since certified cases of pituitary tumor associated with long continued polyuria show the posterior lobe of the pituitary gland to be invariably involved by the process (Kennaway and Mottram, 6), characteristic disturbances of sugar metabolism might be expected in diabetes insipidus. Accordingly, we have studied a number of cases of this condition with this point in view. A survey of the literature (7) indicates that changes in the sugar curve in diabetes insipidus have been somewhat neglected as compared with other pituitary disturbances. In this paper, we present sugar curve data in seven cases of diabetes insipidus (one with co-existing diabetes mellitus), two cases of habitual polydipsia and polyuria, and of four normal subjects who drank water in excess just before and during the tests.

In an earlier paper, Gibson and Martin (8) gave 100 gm. of glucose in a case of diabetes insipidus; blood sugars before and

two hours after the sugar was given were 93 mgm. and 92 mgm. respectively by Benedict's picric acid method. This was a severe case with a urine output of about 25 liters a day. In a metabolic study of a patient with diabetes insipidus, Rabinowitch (9) ran a double sugar curve test (Hamman and Hirschman, 10), giving 100 gm. of sugar at 8 a. m. and again at 12 m.; hourly blood sugars were 125, 206, 168, 120,, 196, 162, 126, one plus qualitative tests for sugar being obtained for urine specimens voided the first and second hours after each ingestion of glucose. Major (5) mentions a case of diabetes insipidus with a fasting blood sugar level of 138 mgm. and a value of 157 mgm. at the end of four hours. Two subjects of diabetes insipidus (one recovered) included in John's (11) series of glucose tolerance tests show low or normal curves. Lawrence and Hewlitt (12) ran a glucose tolerance test with blood sugar determinations on both arterial and venous samples on a young man with diabetes insipidus given 50 gm. of glucose by mouth and 0.75 cc. of pituitrin 15 minutes before the test; their figures show a rather flat curve for the control with a slightly higher peak after pituitrin.

The patients which we have studied all received 50 gm. of glucose by mouth after a 15 hour fast except Subject 1, who received 100 gm. We have established 50 gm. of glucose for sugar curves on adults for our routine tests for the past three years. There is seldom nausea; removal of the gastric contents at the end of two hours in a series of cases has shown that all of the glucose leaves the stomach in that time, and this amount of glucose given intraduodenally gives essentially a similar curve (Magers). Pituitrin was administered hypodermically or by nasal spray (Blumgart, 13). as indicated in Table 1. Blood sugars were on capillary blood from the finger tip by the procedure of Boyd and Gibson (14), samples were taken at half hour intervals. It may be said that in the three years we have been using this technique, we have not observed the abrupt variations in sugar curves recently reported by Gilbert, Schneider and Bock (15).

Of the seven subjects with diabetes insipidus, six have shown a markedly increased and a persisting high blood sugar curve of the type found in diabetes mellitus. Sugar appeared

in the urine in only one of the five, and then in small amounts; this case is that of a diabetic with a co-existing diabetes insipidus. The remaining case (Case 6), that of a patient with a fasting blood sugar of 124 mgm., shows a variation of only 8 mgm. for the first two hours, then dropping to 100 mgm. at 2.5 hours, certainly an increased tolerance. We have earlier data on Subject 5; a test with 100 gm. of glucose (Dec. 6, 1923) induced a blood sugar of 500 mgm. at 3 and 3.75 hours with sugar in the urine for the third and fourth hours.

TABLE I
BLOOD SUGAR CURVES IN DIABETES INSIPIDUS CASES

Case	—Bl. sug. mgm. p. c. at half hrs.—							Urine vol. hrs.			Remarks
	0.0	0.5	1.0	1.5	2.0	2.5	3.0	1	2	3	
1 E. H. m. 19.	100	210	251	250	308	305	350	Glucose 100 gm.
								1002	1002	2-10-1923.
	102	180	240	221	224	85	55	Pituitrin, hypo.
2 M.W. f. 15								1008	1011	2-14-1923.
	80	140	190	149	140	158	138	1850	Urine for 3 hrs.
3 I. J. f. 69								...	1001	9-9-1925.
	172	208	280	311	335	330	306	D. mellitus. Urine sug.
											1 plus. 1-18-1926.
	165	223	311	340	342	320	307	75	175	210	Pituitrin, nasal spray.
								1006	1003	1002	2-1-1926.
	136	182	258	311	280	179	145	360	110	330	Insulin, units 20.
								1001	1002	1001	5-14-1926.
4 J. R. m. 64	136	243	311	330	342	350	360	55	45	40	Pituitrin, hypo.
								1009	1011	1012	5-17-1926. Urine sug. tr.
	130	223	262	311	324	362	377	220	80	470	Urine sug. tr.
								1001	1001	1001	5-20-1926.
5 A. L. f. 46	145	290	323	262	200	143	140	250	110	Sarcoma, orbit.
								1003	1001	1-27-1926.
	119	262	254	205	150	136	110	55	100	260	Pituitrin, nasal spray.
6 H. O. f. 11								1008	1006	1001	1-29-1926.
	155	172	254	311	290	280	249	330	520	Syphilis.
								1001	1001	4-19-1926.
	186	239	324	336	311	300	280	25	40	55	Pituitrin, hypo.
7 H. C. m. 27								1015	1016	1020	4-24-1926.
	138	155	202	255	260	270	215	320	260	250	Insulin, units 15.
								1002	1004	1001	4-29-1926.
8 H. O. f. 11	124	127	125	119	122	100	...	315	125	205	
								1004	1006	1005	12-13-1924.
	115	198	162	133	111	102	96	1150	1500	1140	
								1001	1000	1000	6-18-1926.
9 H. C. m. 27	120	179	190	130	123	76	74	70	65	40	Pituitrin, hypo.
								1020	1020	1015	6-21-1926. Sugar, tr.
	105	158	155	128	86	79	86	215	190	80	No pituitrin.
								1005	1006	1002	6-23-1926.

Partial or complete control of the polyuria with pituitrin has little or no influence on the blood sugar curve in cases of low glucose tolerance. Of four of our cases, two (1 and 4) show a lowered course and two (3 and 5) a contrary effect.

Two habitual excessive water drinkers gave curves similar

in character to those of the five subjects of diabetes insipidus, above mentioned (Table 2). These were differentiated from true diabetes insipidus cases by absence of nycturia with early morning specimens normal in color and concentration. Control of the polyuria with pituitrin and by restricting the fluid intake before and during the test resulted in essentially normal curves for the one case studied (Case 8).

TABLE II

BLOOD SUGAR CURVES IN HABITUAL POLYDIPSIA AND IN NORMAL SUBJECTS DRINKING EXCESSIVE AMOUNTS OF WATER.

Case	—Bl. sug. ingm. p. c. at half hrs.—							Urine vol. hrs.			Remarks
	0.0	0.5	1.0	1.5	2.0	2.5	3.0	1	sp. gr.	2	
8 F. S. m. 30	136	234	290	249	179	143	123	300	350	100	Psychoneurosis. Urine sug. tr. 1-28-1926. Pituitrin, hypo. 2-1-1926. Water withheld. 2-6-1926.
	86	125	172	132	127	105	69	1000	1003	1001	
								25	30	35	
	119	134	137	133	71	119	123	1024	1020	1018	
9 G. McW. f. 44								58	80	30	Mastitis. 2-5-1926.
								1013	1006	1015	
	121	213	311	213	120	83	93	380	490	220	
								1001	1001	1001	
10 R. G. m. 44	129	234	223	140	93	94	119	475	750	600	Normal subject. 2-5-1926. Control exp. 2-24-1926.
								1001	1001	1001	
	95	155	129	117	75	77	86	60	140	50	
								1012	1008	1012	
11 W. S. m. 53	121	194	119	81	88	93	105	100	215	60	Normal subject. 2-19-1926. Control exp. 3-6-1926.
								1010	1003	1012	
	127	137	126	104	84	106	104	
12 H. D. m. 26	103	140	123	102	88	103	93	190	775	570	Normal subject. 2-17-1926. 2-24-1926.
								1003	1000	1001	
	70	145	105	74	56	52	55	750	850	350	
								1001	1001	1001	
13 E. M. f. 28	119	198	172	102	119	109	84	1120	1120	480	Normal subject. 5-4-1926. Control test.
								1001	1001	1001	
	110	155	120	123	77	102	96	

The effect of excessive water intake on the sugar curve was then studied in four normal individuals (Table 2) who were instructed to drink two glasses of water on arising and a glass every half hour thereafter until the test was completed. Two of the subjects (10 and 13) show a distinct lowering of tolerance with blood sugar curves which rose rapidly but have dropped to the fasting level in two hours; a third (11) gave a single high spike at the half hour (a polyuria was not well established), and the fourth (12) had a normal result in two trials, though at different levels.

High renal thresholds obtain for the habitual and experimental water drinkers just as for subjects of diabetes insipidus. Traces of sugar were found in Case 8 only.

Insulin was administered 15 minutes before glucose was given to subjects 3 and 5. While the whole sugar curves were lowered as a result, a very diminished tolerance was still evident. In view of a suggested antagonistic action of insulin and pituitrin (13) a much more pronounced effect would be expected from insufficiency of the posterior lobe.

The presence of co-existing diabetes mellitus and diabetes insipidus in one of our patients warrants a further discussion of this case. We have found only one reference in the literature, a case reported by Lauter and Hiller (16) in which the highest blood sugar was but 128 mgm. per cent. A summary of the clinical findings in our case follows:

Case 3. Mrs. I. J., age 69 was admitted to this service first on September 18, 1923. She complained of weakness, loss of weight from 180 to 118 pounds, polyphagia, polydipsia, and polyuria with glycosuria, and an attack of blindness with gradual onset and recovery. Her blood pressure was 116/68, and blood drawn for a Wassermann test was negative. Her urine for the first day of management had a specific gravity of 1.020, 2.3 percent of sugar with a total output of 45 gm. on a diet with a glucose value of 79 gm. Her blood sugar the second day of management was 357 mgm. She responded in the usual way to a restricted dietary regime, becoming sugar-free on the fifth day and with a blood sugar of 128 mgm. 2 hours after breakfast on the seventh day. Her urine volume ranged from 1800 to 4300 cc. with specific gravities of 1.002 to 1.005 after she was desugarized. From her history, laboratory findings, and with an ordinary response to diabetic management, a diagnosis of diabetes mellitus is unquestioned. Blood uric acid and urea nitrogen were normal. Ophthalmological examination gave no reason for the blind spell reported, but the patient showed an asteroid hyalitis which still obtains.

On the sixteenth day the urine volume suddenly more than doubled and blood sugar rose to 200 mgm. The daily amounts of urine ranged from 6 to almost 9 liters a day. Insulin, 30 (old) units a day was without effect on the polyuria when given with additional carbohydrate for three days. After ten days, the urine volume dropped to about 4 liters daily, specific gravity 1.003; and with 15 units of insulin a day, the blood sugar fell to 111 mgm. Insulin therapy was discontinued, the polyuria further diminished, specific gravities from 1.007 to 1.013 are in her record, and she was discharged on a maintenance diet with a blood sugar of 120 mgm. on November 9, 1923.

The patient was again admitted to our service February 16, 1924 for observation. Her urine was free from sugar; volumes from 1300 to 2650 and specific gravities of 1.005 to 1.013 are noted. Blood sugar on admission was 227 mgm., but this dropped to 125 mgm. with hospital management, and the patient was discharged March 4th, 1924 on a slightly increased diet.

She was unable to carry out dietary control satisfactorily at home and returned to the hospital on June 25, 1924. On the first full day of management on a maintenance diet, the urine volume was 1400 cc., specific gravity 1.016, urine sugar 0.95 percent and 13.8 gm., with a blood sugar of 454 mgm. The urine contained traces

of sugar until the tenth day, blood sugars remained high, urine volumes were not excessive and specific gravities of sugar-free urine were as high as 1.017. A basal metabolic rate determination at this time was minus 4 percent.

She was admitted for the fourth time, May 1, 1925 with small amounts of sugar in the urine, but with the polyuria reestablished. The urinary sugar cleared up under dietary management, blood sugars remained high, 182 mgm., when given 15 units of insulin a day after desugarization of the urine without insulin. The polyuria was partially controlled with pituitrin given by nasal spray. The patient's skull, when x-rayed, was normal except for an increase in density 1 cm. in diameter and 6 cm. above the sella.

She has been admitted three times during the past year with a polyuria of from 4 to 6 liters daily and characteristically low specific gravities. Courses of insulin treatment with special reference to checking the polyuria (17) continue ineffective; the use of pituitrin by nasal spray keeps her volume excretion within comfortable limits.

SUMMARY

Five out of six subjects of diabetes insipidus have responded to a glucose tolerance test with blood sugar curves of a diabetes mellitus type, but with high renal thresholds for glucose. The curve was not influenced consistently when the polyuria was controlled with pituitrin; two curves were slightly higher and two somewhat lower.

One subject showed an abnormally flattened curve.

One subject with diminished tolerance exhibits an unquestionable diabetes mellitus as well. Insulin lowered the curve in this case and in one other case tried, but diminished tolerance is still pronounced.

Two habitual water drinkers gave high persisting blood sugar figures quite similar in character to the curves in the diabetes insipidus cases. In the one patient further studied, both pituitrin and control of the polyuria by limiting the fluid intake resulted in normal curves.

Three out of four normal subjects who drank water excessively before and during the tests showed high blood sugar values as compared with control curves, though the figures fell to normal or below at the end of two hours. An increased renal threshold is indicated also.

A summary of the history of the subject with co-existing diabetes insipidus and diabetes mellitus is included.

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Book Reviews

KLINISCHES LEHRBUCH DER INKRETOLOGIE UND INKRETOTHERAPIE.
Ed. by Gustav Bayer and R. von den Velden. Pp. 423. Leipzig, 1927. G. Theim.

The book represents a more or less conventional text-book treatment of the subject matter of endocrinology. It includes several sections by different authors.

An historical introduction by Richard Koch occupies 12 pages, of which three are devoted to a representative bibliography.

The anatomy, physiology, pharmacology and pathology of the endocrine organs are treated by Bayer in a section of 120 pages. It is, on the whole, the most satisfactory in the book, being for the most part judicious and clear. The chief defect of the chapter is the reiteration of a considerable amount of venerable mythology on the thymus gland. Two dubious statements are that some of the nerve fibers to the thyroid gland are certainly secretory and that pituitary extract is a powerful galactagog. Among the numerous commendable features is the use of the word "parasympathetic" instead of the confusing teutonism, "autonomic." The bibliography comprises twenty-five citations, mostly synthetic monographs by well selected authorities. Eight of these are non-German. Whatever may be the disadvantages of setting forth the literature at third hand, the method has the advantage of bringing together a jury of experts on the subject matter treated.

The chapter on diagnosis (22 pages) by Velden includes an interesting summary of the better known diagnostic methods and a scheme for dealing with "constitutional" data. The subject of general organotherapy is treated by the same author. This chapter is rather more philosophic than practical.

The next chapter (55 pages), on typical endocrine pictures, is by Leo Borchardt. The point of departure for the section on the thyroid is Kocher's well known but misleading table of contrasting symptoms of hypo- and so-called hyper-thyroidism. As a result the thyrotoxic picture is quite inadequately drawn. No distinction is made between toxic adenoma and exophthalmic goitre. Neisser's "pioneer" work on the use of iodine in Grave's disease receives some attention but its theoretical significance is missed. In this connection it is indicated that Plummer and

Boothby "of Chikago" have also contributed. As regards the adrenals it is noted that "Kowntree" saw some good results from the systematic use of adrenal preparations in Addison's disease. The chapter runs on in safe and sane channels until the subject of pluriglandular syndromes is reached—on which subject one man's guess is about as good as another's. The chapter concludes with a bibliography of 77 citations including one each from England, France, Italy, Scandinavia and America.

The rest of the book, some 200 pages, is devoted to a rehashing of the ordinary subject matter under the captions: endocrine "moments" in internal medicine, psychiatry and neurology, pediatrics, and various other of the recognized medical specialties. For endocrinologists this arrangement seems stilted and for the specialists, rather out of focus. Of these chapters, that by Edwin Schiff on pediatrics appeals as most worth while, perhaps because there is a considerable body of well established data common to, and well organized, in, the two fields. Bernard Aschner's chapter on gynecology is also deserving of favorable comment. His bibliography, incidentally, is one hundred per cent pure German.

The book closes with an index of 20 pages.

To those desiring a discussion of the German contributions to endocrinology, the book is commended as well balanced, mostly sound, easily readable and entertaining. Those desiring, however, a picture of endocrinology in international perspective might well look further.

HANDBUCH DER INNEREN SEKRETION. Ed. by Max Hirsch. Vol. 1, Pt. 1, Pp. 196. Leipzig, 1926. C. Kabitzsch.

According to the prospectus the handbook will appear in three volumes devoted, respectively, to normal and pathological morphology, normal and pathological physiology and clinical pathology and therapy. Each section will be made up of several parts, published and sold separately.

Part 1 of Volume 1 begins with an introductory section of 24 pages by the Editor. Judging by the bibliography it consists largely of a rehashing of historical articles by other German writers.

The next section, of 98 pages, on the pancreas is by G. Herxheimer. It might well serve as a model for the other contributors to the handbook. It is clearly written, concise and broadly based on the world's literature. The illustrations, mostly in color, are noteworthy. The topics treated are: normal morphology, pathology in relation to internal secretion, transitional relationship of zymogen and insular tissue, relationship of the pancreas to diabetes, pancreatic disorders inducing diabetes.

and changes in other organs in diabetes. The bibliography includes 800 or more citations covering the outstanding works appearing in English, French, German and Italian. Modern bibliographic style is for the most part followed, though now and again an incomplete citation appears. The chapter is admirable throughout.

The volume concludes with a section of 74 pages by W. Lahm on the female sex organs. This takes up in order the morphological features of the ovary, uterus, vagina, clitoris, placenta and mammary glands. There is no obvious reason—and no adequate reason is supplied in the text—for the inclusion of the birth canal, the clitoris and the mammae as endocrine organs. The broad ligament fortunately was omitted. The section devoted to the ovary is the most extensive and the best of the chapter. The normal conditions of this structure in the embryonic, infantile, adult and senile epochs is discussed together with ovarian changes following radiation, choline sterilization and hysterectomy and in gynecological diseases. The author makes a rather feeble excursion into physiology to discuss the effects of ovarian extracts. The significant recent work on this topic is rather consistently missed. The discussion of the placenta is brief but covers rather well what morphological evidence we have as to its possible endocrine function. The discussion of placental extracts is entirely inadequate and out of place in this chapter. The bibliography of some 250 citations, only, is far from creditable. Aside from a few original articles in French, the material has been gathered apparently entirely from German sources, and these largely abstract journals. The citations are incomplete and inconsistent and the foreign titles often garbled into German. The fact that so important an authority as Marshal is cited only at second-hand tells much.

The handbook promises to be a very useful addition to the literature but it is to be hoped that subsequent contributors will realize that a large proportion of the best endocrine work has emanated from other than German sources.

Abstract Department

Variations of the pH of the blood and the response of the vascular system to adrenalin. Burget (G. E.) & Visscher (M. B.), *Am. J. Physiol. (Balt.)*, 1927, **81**, 113-123.

Levy has reported that stimulation of the cervical sympathetic results in augmented reactions to repeated doses of adrenalin. This augmentation disappeared after thyroidectomy. Upon further investigation of this phenomenon Burget and Visscher found that in the pithed cat, when the artificial respiration is constant, small intravenous injections of adrenalin do act with progressively increasing effectiveness, but only provided the pH of the blood is rising. The secretion of the thyroid plays no part in this reaction. Such increasing responses to adrenalin are not due to the drug sensitizing the sympathetic nervous system. The adrenalin response of the vascular system of the pithed cat may be made to vary at any time by varying the pH of the blood. From pH 6.9 to 8.0 the response progressively increases. The most effective means of varying the pH within this range is by varying the amount of air carried to and from the lungs. Acidosis caused by acids other than carbonic is not overcome by increased aeration, nor do animals showing such acidosis give increased responses to repeated injections of adrenalin. The increased response seems to be due either to an increased irritability of the sympathetic nervous system because of an increase in the pH of the blood, or to the possibility that, as the pH of the blood rises, adrenalin is oxidized more rapidly and completely and thus constitutes a stronger stimulus at its seat of action, the irritability of the myoneural junction remaining constant.—R. G. H.

Kidney function in adrenal insufficiency. Hartman (F. A.), MacArthur (C. G.), Gunn (F. D.), Hartman (W. E.) and MacDonald (J. J.), *Am. J. Physiol. (Balt.)*, 1927, **81**, 244-254.

Blood changes have been followed in adrenalectomized cats, some of which survived more than 35 days. Details are presented for four animals. There was increase in the blood solids. The blood sugar fell in the later stages, reaching as low as 50 per cent of the normal at death in some individuals. The calcium, creatinin and uric acid in the blood were slightly above normal. The acid-soluble phosphates of the blood were considerably higher than

normal in the later stages. The blood urea increased and this increase to some extent ran parallel with the loss of appetite and other symptoms. The ingestion of liver caused a marked increase in blood urea and an exacerbation of the symptoms. The anatomical changes, which appeared rather constantly, were: purplish discoloration of the gums, hemorrhages in the thymus, general hyperemia of the internal organs and an accumulation of large quantities of lipoid substances in the tubuli contorti.—R. G. H.

On the transplantation of the guinea pig suprarenal and the functioning of the grafts. Jaffe (H. L.), J. Exper. M. (N. Y.), 1927, 45, 587-594.

The author removed the right suprarenal in 22 young guinea pigs and transplanted it immediately into the abdominal muscles. Before transplantation the gland was cut into 8 to 16 sections. The epinephrine-containing tissue was dissected away, after which the cortical tissue was washed in physiological saline solution before transplantation. The latter was effected by the introduction of the sections into small pockets made in the muscle. Three to 7 weeks later, the left suprarenal was removed. The animals were then observed over periods varying from 3 to 276 days, at the end of which the auto-transplants were studied microscopically in serial sections. While many of the animals died from suprarenal insufficiency, those that survived were maintained in good condition. The auto-transplants grew to fairly large size and were found to consist of normal cortical cells. Most of the homotransplants showed evidence of degeneration.—I. M.

The action of adrenalin in association with a complete diet (Tier-experimentelle Untersuchungen über die stoffwechsel-physiologische Wirkung bestimmter Hormone. III. Die Wirkung des Adrenalins bei Verabfolgung von stofflich und kalorisch vollwertiger Nahrung). Junkersdorf (P.) & Schüler (H.), Arch. f. d. ges. Physiol. (Berl.), 1927, 216, 549-554.

The most marked effect is an almost complete disappearance of muscle glycogen in presence of high liver glycogen content.

—A. T. C.

Lipoid metamorphosis of two suprarenal glands with melanoderma (Metamorphose adipeuse des deux capsules surrenales avec melanoderma). Loeper (M.) & Ollivier (J.), Bull. et mém. Soc. méd. d. hôp. de Par., 1926, 8, 312-316.

The authors report a case of a woman 31 years old with typical symptoms of Addison's disease. Autopsy revealed marked involvement of the adrenals but no sign of tuberculosis. The adrenals, while maintaining their form, were reduced to oily masses. On section certain areas appeared dense and a little darker than

the surrounding tissue. The gland on the left side, less diseased, had about 1 cm. of recognizable gland tissue. After hematoxylin-eosin stain, reddish islands of fat and oil-like areas appeared on the border. In slightly larger sections, hollowed out areas were present with a number of vacuolized edges which blended with the cellular lipoid. These cellular islands were rather homogeneous and somewhat translucent, engulfing one another, without perceptible capillary formation or formation with glomeruli or fasciculi. The interior of the islands, interspaces and peripheral portions showed no evidence of sclerosis, lymphatic reaction, infection, caseous degeneration or giant cells. There were a few polymorphonuclear leucocytes and capillaries or blood vessels containing a small quantity of blood and in only one place some lymphocytes. A few nerve filaments were present which did not appear in the intact lipoid which was more marked in the right gland than in the left. In the latter some adrenal tissue was present but without sclerosis, infection or infiltration of any sort. It was concluded that this adipose evolution of the glands was due to a congenital malformation.—R. C. Moehlig.

Calcification of the suprarenal glands of cats. Marine (D.), *J. Exper. M.* (N. Y.), 1926, **43**, 495-499.

The author observed calcification of the suprarenal cortex in 64 out of 257 cats examined. This was more commonly seen in young than old animals. The only etiological agent found to be of importance was distemper. Attempts at production of similar calcification by means of diphtheria toxin, arsenic, ethyl chloride freezing, ligation of blood vessels and trauma were unsuccessful. It has not been found following other types of infection such as chronic pneumonia or wound infections. Bone formation did not occur. The symptoms referable to the lesion were those of suprarenal insufficiency. In a series of 328 dogs, 2,300 rabbits, 150 pigs, 200 sheep and 125 cattle no calcification was found. Occasional cases of suprarenal calcification have been described in man.—I. M.

Duration of life after suprarenalectomy in cats and attempts to prolong it by injections of solution containing sodium salts, glucose and glycerol. Marine (D.) & Baumann (E. J.), *Am. J. Physiol.* (Balt.), 1927, **81**, 86-100.

Eighteen control cats from which both suprarenals were expeditiously removed at one operation survived on an average of 5.3 days. These are claimed to be the best results in cats yet secured. (See Hartman, et al., this issue). The administration of physiological salt solution, Ringer's solution and isotonic sodium acetate solution (49 cases) increased the duration of life to about three times that of the controls. More concentrated solutions of sodium chloride slightly shortened life (4 cases). Isotonic glucose

and glycerol solutions had only a very slight life-prolonging effect (12 cases). It may be concluded from these studies that diuresis is one of the important factors determining the duration of life. When the loss of water by diuresis is compensated for by an additional intake, life is prolonged, and if not, life is shortened. There is some indication that the loss of sodium is more specific than can be accounted for as a result of a possible acidosis. The authors believe that all the results of adrenal ablation thus far observed are the individual details of a more fundamental and as yet unknown disturbance in nutrition in which the sympathetic nervous system is primarily concerned.—R. G. H.

Sensibility of rats to cold after adrenalectomy (*Sensibilité au froid des rats decapsules*). Marvel (L.), *Rev. Soc. Argent. de biol.* (Bs. Aires), 1926, 2, 226-231.

Three groups of rats were studied—the first group with bilateral adrenalectomy, the second with single and the third with a sham laparotomy as controls. When the first group was kept for a short time at 10° to 15° their rectal temperature fell to 34°, but it required 15 to 20 days after returning them to a temperature of 25° to restore their body temperature to that of the controls. When all were placed in a refrigerator for one hour, the rats adrenalectomized bilaterally had a terminal descent more marked than the singles or the controls. With the passage of time the rats became less susceptible to cold, due perhaps to hypertrophy of accessory adrenal tissue.—E. W. E. Schear.

A quantitative comparison of epinephrin and ephedrin. Nadler (J. E.), *J. Pharmacol. & Exper. Therap.* (Balt.), 1927, 30, 489.

Using the chromatophores of the squid for test material, the author compared the potency of these two substances in antagonizing the action of parathyroid extract, antuitrin, postuitrin and BaCl₂, by subcutaneous injection. The minimum effective dose of epinephrine was found to be 0.8 cc.; of ephedrin, 2 cc. Epinephrine was more effective in antagonizing all substances except BaCl₂, in which case ephedrin was nearly 10 times as effective.—C. I. R.

Vagotropic influence of adrenalalin (*Ueber die vagotrope Wirkung des Adrenalins*). Smirnow (A. J.) & Schiroky (W. F.). *Ztschr. f. d. ges. exper. Med.* (Berl.), 1927, 55, (1/2), 24-34.

Observations on the well-known slowing of the heart after intravenous epinephrin injections. After transection of the cord in the neck, cardiac slowing was obtained from epinephrin before the pressure rose from its initial low level to the height at which reflex slowing is believed to occur. This is the argument for the conclusion that epinephrin stimulates the vagus center directly. Dogs.

cats, and rabbits were used, but the phenomenon was observed regularly only in dogs and not at all in rabbits. A preliminary injection of morphine was used to increase the tonus of the vagus center. Magnesium is antagonistic to the vagotropic action of epinephrin.

—E. E. Nelson.

X-rays and adrenalin in blood (*Action des rayons X sur l'adrénalinémie*). Zunz (E.) & La Barre (J.), *Compt. rend. Soc. de biol. (Par.)*, 1927, **96**, 126; *Abst., Physiol. Absts.*, **12**, 173.

By a cross-circulation method in dogs it is shown that irradiation with hard x-rays produces a release of adrenalin from the adrenal gland.

The relationship of hypothalamus centers to blood pressure and internal secretion (*Ueber Beziehungen der Hypothalamuszentren zu Blutdruck und innerer Sekretion*). Karplus (J. P.) & Kreidl (A.), *Arch. f. d. ges. Physiol. (Berl.)*, 1927, **215**, 667-670.

After extirpation of the pituitary and the adrenals the effect of stimulation of the hypothalamus centers in producing a rise of blood pressure is unaffected.—A. T. C.

The endocrines in epilepsy: a histological study. Schou (H. I.) & Susman (W.), *Brain*, (Lond.), 1927, **50**, 53-59.

Six epileptics, dead from various causes, were examined histologically, though all the glands from each case were not available. No distinctive lesions of the gonads were seen. If the cause of death was an acute infectious disease the thyroid showed the usual acute reaction, but otherwise there was no distinct lesion. Active degeneration was observed in one gland, and in another a pronounced fibrosis. In some of the adrenals a picture of slow chronic inflammation was seen. All of four anterior pituitaries examined showed marked enlargement. In both adrenal medulla and anterior pituitary the destructive agent especially attacked the chromophil cells. Three pancreases showed uniform abnormality. Only a negligible number of islets showed recognizable signs of degeneration, but abundant hypertrophied islets occurred and mitosis in islet cells was frequently seen. All the external parathyroids were enlarged, and showed abundant oxyphilic cells. A corresponding examination of endocrine glands from patients that had died from the common prostrating and infectious diseases showed no such lesions.—A. T. C.

The therapeutic action of roentgen rays on glands of internal secretion (*Zur Therapie der Drüsen mit innerer Sekretion in der Roentgenologie*). Wieser (W. F.), *Acta Radiologica* (Stockholm), 1926, **7**, 646-674.

The results of x-ray treatment of the endocrine glands vary

considerably. History and clinical methods of investigation give on the whole no information. The ferment reaction of Abderhalden permits determination of the quantitative function of each individual gland, while the estimation of the exchange of gases, by help of the information gained by the former, informs us about the nature of the disturbance. With the aid of both of these methods we are able to determine which gland is at fault, and what dosage is required, according to the strength of the reaction, or at least, whether an overdose or an underdose has been given before the onset of clinical symptoms. In addition, we can clear up the relation between the main disease and adjunct conditions. The two modifications of the Abderhalden method are the refractometer of Pregel and the interferometer of Hirsch. The former should be used only when little serum is available, while the latter is more precise. The methods do not enable one to establish a clinical diagnosis. The practical results of 32,000 investigations on 580 patients and the subsequent treatment evolved of 360 patients may be summarized as follows:

Similar results are obtained with patients at different times when the degree of sickness remains the same. In diseases running a definite course the reaction is accurately correlated to the phase of the illness. It has also a similar relationship to the clinical condition and to the result simultaneously obtained from the exchange of gases. Similar body conditions give similar reactions. A better or worse clinical condition corresponds with a higher or lower value of the reaction; similar clinical conditions, provided the cause of the disease is the same, give similar reactions. The therapy founded upon these methods of investigation gives good results with few exceptions (only 4.8 percent) in mongolian idiocy and other types of idiocy.

The author explains the exceptions by claiming that they occur in conditions present in addition to the principal disease and which affect the endocrine system but which must be treated later. Good therapeutic results can be obtained in tuberculosis, syphilis, gonorrhea, functional disturbances of the kidneys, chronic forms of encephalitis, as well as in other toxic or exhausting disorders which produce a chronic irritation of the endocrine glands. The interpretation of the results is not easy as a reaction is obtained only in cases of hyper- and non-functioning of a diseased gland. In those instances where there is just a lowering of function we get a stronger reaction in the substituted and overactive glands. Clinical observation will then supply the explanation in most cases.

—M. B. G.

Structure of the cells of the human corpus luteum, and its changes during the cycle of menstruation and pregnancy (Über die Struktur in den Corpus luteum-Zellen des Menschen und ihre Veränderungen während des Menstruationszyklus und bei Gravidität).

Chydenius (J. J.), Arb. Path, Inst. Univ. Helsingfors, 1926, 4, 320-414; Abst., Biol. Absts. 1, 272.

The detailed structure of the human corpus luteum was studied from 30 operative cases. In every instance full anamneses of menstruation were available. Histological examination of the mucous membrane of the uterus was made in many cases. Despite a rather distinct regularity in the relations between the ovarian and the uterine cycles of menstruation, the author points out that from a histological parallel examination of the operative material an unambiguous solution of the problem of the connection between the formation of corpus luteum and the uterine cycle is not to be expected. The structure of the cell body is emphasized. The structures examined (microcentrum, structures which can be impregnated with silver, chondriosome apparatus), and changes in them in different stages of development of the corpus luteum are described and 17 figures given. Progressive development can be observed in the structure of the cell body of the granulosa lutein cells, which has no analogy in the theca lutein cells. A special study was made of regressive changes in the cell body in the "regressive stage" of the corpus luteum cells. These are rich in lipoids, hence this characteristic can not be regarded as indicative of the augmented functional activity.

Quantitative action of the follicular hormone (Sur l'action quantitative de l'hormone folliculaire). Courrier (R.), Compt. rend. Acad. d. sc. (Par.), 1926, 182, 1492-1494; Abst. Physiol. Absts., 12, 116.

Varying amounts of sow's liquor folliculi were injected into female guinea-pigs of the same age and weight, which had been castrated at the same date. After 46 hours the animals were killed; histological examination of the vaginal epithelium showed mitotic division in all cases, but the intensity and time of reaction was found to be unaffected by the dose received.

The uterine reaction to the injection of liquor folliculi in castrated rabbits (Réaction utérine chez la lapine castrée a l'injection de liquide folliculaire). Courrier(R.) & Potvin (R.), Compt. rend. Soc. de biol. (Par.), 1926, 94, 878-879; Abst., Biol. Absts. 1, 279-280.

A virgin female rabbit was spayed at the age of 5 months. Five weeks later one horn of the uterus was removed and found to be very small, flattened, atrophic and with the usual glands very poorly developed. Three days later the daily injection of 2.5 cc. of liquor folliculi from the ovary of a cow was begun and continued for 7 consecutive days. Autopsy at this time revealed the remaining horn of the uterus much hypertrophied and congested,

quite similar in appearance to the uterus of a normal doe during oestrus.

Hormonal sterilization of female animals. III. Feeding experiments with ovarian and placental optones (Ueber hormonale Sterilisierung weiblicher Tiere. III. Füttersversuche mit Ovarial- und Placenta-Optons). Haberlandt (L.), Arch. f. d. ges. Physiol. Berl.), 1927, 216, 525-533.

Such feeding produces sterility in white mice.—A. T. C.

Menstrual records and vaginal smears in a selected group of normal women. King (Jessie L.), Carnegie Inst. Washington Publ., 1926, 363, 79-94; Abst., Biol. Absts. 1, 280.

The menstrual histories and dates of the periods of 17 women are given. Twenty-seven days is the most frequent of the 523 intervals recorded. The records strongly support the statements regarding variability in the length of the cycles. Seven members of the group made vaginal smears daily for periods covering 2 or more intervals each. There is great variation in the cellular content of these series and they do not indicate that changes in the human vaginal secretion serve as an index of periodic changes transpiring in the ovary and uterus.

Internal secretion of the ovary. Pratt (J. P.), Ann. Clin. M. (Balt.), 1927, 5, 663-670.

Evidence that there is an internal secretion of the ovary is briefly reviewed. Inter-relation of the ductless glands is emphasized, especially the influence of the thyroid on disturbances of menstruation. An identical hormone has been prepared from Graafian follicles, corpora lutea, and placenta. This hormone, when injected into spayed animals, substitutes for the ovarian function and reproduces all phases of oestrus, but does not substitute for ovaries in women to the extent of bringing on menstruation. The most striking effect in women is shown in the improvement of irregular and scanty menstruation.—Author's Abst.

The sexual hormone and secondary sexual characteristics of the fowl: II. Relation of castration and transplantation of testicles (Les caracteres sexuels secondaires chez les gallinaces et l'hormone sexuelle. II. Rapports de la castration et de la transplantation des testicules avec les caracteres sexuels males). Sakamoto (S.), Folia Endocrinologica Japonica (Kyoto), 1926. 2 (V), 33-36.

By castrating fowls after puberty Sakamoto noticed that the comb, wattles and tufts began to grow smaller and to atrophy. The plumage and spurs did not change. The fowls became listless,

they issued only a monosyllabic cry and the sex and battling instincts disappeared. In complete pre-puberal castration the comb and wattles did not develop, neither did the fighting instinct, sexual desires or challenge appear. In complete castration the birds became normally adult after 28 to 105 days.—L. L. Stanley.

The nitrogen metabolism of eunuchs. Shen (T. C.) & Lin (K. H.), Chinese J. Physiol. (Peking), 1927, 1, 109-122.

Nine healthy eunuchs, from 38 to 57 years of age, and castrated at least 25 to 30 years previously, were investigated. No appreciable difference between the total nitrogen excretion in the urine of eunuchs and in that of normal men was found; nor was there an increase in the ammonia output, which has been said to be characteristic of eunuchs. Only one eunuch showed creatine in the urine, and this was but a fraction of its intake. This result is contrary to the generally accepted statement that creatinuria is characteristic of eunuchs castrated before puberty. One eunuch also showed considerable daily variation in the creatinine output, the cause of which was not discovered. This seems to be a violation of Folin's law of the constancy of urinary creatinine. A moderate amount of exercise, as riding on an ergometer half an hour a day, caused a slight decrease of creatine and a corresponding increase of the creatinine in the urine. Three daily periods of maximum excretion of both creatinine and creatine, occurring at 12 noon, 4 P. M., and 8 P. M., respectively, were found in the one eunuch with constant creatinuria. Exercise did not alter these maxima.—L. G. K.

The physiology of the rut of guinea-pigs [Ueber weibliche Sexualhormone (Thelytropine). XIV. Beiträge zur Physiologie der vaginalen Brunstvorgänge des Meerschweinchens)]. Voss (H. E.), Arch. f. d. ges. Physiol. (Berl.), 1927, 216, 156-180.

The frequency and duration of rut in guinea-pigs is not as regular as is usually considered. The interval between the climaxes of two rut periods can vary between 13 and 20 days, the duration of the dioestrus between 9 and 16 days. There appears to be a relationship between the anoestrous and dioestrous periods and the intensity of the following rut.—A. T. C.

Hereditary diabetes insipidus. Chase (Lillian A.), Canad. M. Ass. J. (Montreal), 1927, 17, 212-214.

A case of diabetes insipidus is reported in a man aged 36. He showed satisfactory improvement, possibly due to the action of pituitrin, but more probably to an outdoor life. The disease was traced through five generations, and shown to be dominant, and not sex-linked.—A. T. C.

Studies in acromegaly. IV. The basal metabolism. Cushing (H.) & Davidoff (L. M.), *Arch. Int. Med. (Chicago)*, 1927, **39**, 673-697.

Acromegaly is often accompanied by an elevated basal metabolism rate and the reverse condition of hypopituitarism by a sub-normal rate. Acromegaly is also often accompanied by an enlarged thyroid and by symptoms suggesting thyreotoxicosis. In three cases of acromegaly with goiter subtotal thyroidectomy lowered the basal metabolic rate. The gland in these cases showed only colloid changes of the adenomatous type without evidence of toxicity. Iodine medication also lowered the basal metabolic rate. Operations on the chromophilic hypophysial adenoma itself in cases of acromegaly with elevated basal metabolism are followed by a striking fall in the basal metabolic rate.—M. O. L.

Experimental gigantism—differential effect of anterior hypophyseal extract on normal and gonadectomized males and females. Evans (H. M.) & Simpson (Miriam E.), *Anat. Record (Phila.)*, 1927, **35**, 36-37.

Groups of litter-mate brother and sister rats have been constituted by placing in each group normal untreated, gonadectomized untreated, normal treated, and gonadectomized treated animals. The treated animals received intraperitoneally daily beginning with the twenty-first day of life 1 cc. of the supernatant fluid from a centrifuged neutralized alkaline extract of the anterior hypophysis of beeves. Without treatment, the gonadectomized female is heavier than her control, the gonadectomized male lighter than his control. The same relations are shown when overgrowth is stimulated, the sequence from heavier to lighter animals being: normal males treated, gonadectomized males treated, gonadectomized females treated, and normal females treated. The marked early plateauing of the female growth curve produces a greater contrast at the two hundredth day of life between treated and untreated females than between males at this time.

—Author's Abstract.

Pituitrin and blood lipoids. Gunnar (B.) & Ohlin (C. A.), *Skand. Arch. f. Physiol. (Berl. & Leipz.)*, 1927, **51**, 167-174.

Experiments are reported on 6 rabbits and 3 dogs. Pituitrin was injected subcutaneously in doses of 2 cc. for rabbits and 5 to 6 cc. for dogs. The blood lipoids were determined at intervals of 3, 6, 9, 12 and 24 hours after injection. The phosphatid fraction was found to be regularly decreased, the maximal effect being apparent about 9 hours after injection. The neutral fat temporarily disappeared after the injection. The cholesterol was not affected.

—R. G. H.

The effect of pituitrin administration upon certain phases of carbohydrate metabolism. Hines (H. M.), Leese (C. E.) & Boyd (J. D.), *Am. J. Physiol.* (Balt.), 1927, **81**, 27-35.

Controlled experiments on 6 dogs are reported. It was found that the administration of pituitrin in doses of approximately 0.05 cc. per kilo body weight per hour together with glucose by the continuous intravenous method result in a decreased retention of the injected sugar. There was a greater degree of hyperglycemia and glycosuria than in control experiments on the same animals with glucose alone. Pituitrin administration was without appreciable effect on the respiratory quotient and extra heat produced during the glucose injections. Significant acid-base changes in the blood were not detected. A pituitrin action on the kidney is not regarded as an appreciable factor in these experiments. The evidence for decreased retention of glucose resulting from pituitrin administration appeared early in the course of the experiments and did not appear to be more pronounced at the end of the period. It is suggested that an altered capillary circulation may be an important factor in the mechanism of pituitrin action.—R. G. H.

The relation of kidney excretion in diabetes insipidus to the theories of urine excretion. Observations on the characteristics of urine in diabetes insipidus. Illievitz (A. B.), *Canad. M. Ass. J.* (Montreal), 1927, **17**, 180-184; 424-425.

A contrast was made of the composition of urine in a case of diabetes insipidus with urines in polyuria induced experimentally in normal individuals. The results support the conclusion that the polyuria of diabetes insipidus is due primarily to action of the internal secretion of the pituitary on the kidney (and also favor the theory of secretion through renal cell activity rather than simple kidney filtration).

The subject studied was resting in bed. The urine contained no inositol, no creatine and no creatinine, while there appeared to be a decrease in chloride excretion, and some unknown compound was present which turned purple in the standing urine, and which could not be related to indican. A second case, with a less degree of polyuria, and performing some muscular work, showed presence of creatinine in the urine.—A. T. C.

The experimental feeding of fresh anterior pituitary substance to the hypophysectomized rat. Smith (P. E.), *Am. J. Physiol.* (Balt.), 1927, **81**, 20-26.

Controlled experiments were made on 6 rats from which the anterior and posterior lobes of the hypophysis had been previously removed. It was found that the daily feeding of fresh bovine anterior pituitary glands did not cause any increase in the body

weight, or in the tail or body length. The growth curves of animals thus treated paralleled those of the hypophysectomized rat receiving an equal amount of muscle as a control substance. This anterior pituitary feeding also failed to restore, in the slightest degree, the atrophied genital system, thyroids or adrenal cortex of the hypophysectomized rat.—R. G. H.

Induction of precocious sexual maturity in the mouse by daily pituitary homeo- and hetero-transplants. Smith (P. E.) & Engle (E. T.), *Proc. Soc. Exper. Biol. & Med. (N. Y.)*, 1927, **24**, 561-562.

The acceleration of sexual maturity is even more rapid in the mouse than in the rat. The females respond to the treatment much more rapidly than the males. Transplants from rat, guinea pig and rabbit are effective. The anterior lobe is the portion of the pituitary producing these results.—J. C. D.

Effect of hypophyseal extract on bone development (*Les modifications des cartilages de conjugaison à la suite des injections d'extrait de lobe posterior d'hypophyse chez le cobaye en voie de croissance*). Stefanescu (Marie), *Compt. rend. Soc. de biol. (Par.)*, 1926, **95**, 783-784; *Abst., Biol. Absts.* **1**, 276-277.

Repeated injections of posterior pituitary extracts produced changes in the epiphyseal cartilages in 2 of 5 guinea pigs. In these 2 the cartilages were thinner than normal, contained fewer cells in rows and otherwise gave evidence of reduced proliferation and of precocious ossification. These results seem to show that posterior pituitary extracts retard the growth of bone, confirming Cerletti ('06).

The weight and dimensional effects of anterior hypophyseal extract on the gonadectomized male rat. van Wagenen (Gertrude), *Anat. Record (Phila.)*, 1927, **35**, 51.

The effect of fresh anterior-lobe fluid injected intraperitoneally into gonadectomized male rats was tested and the weight and length correlation made with untreated brothers. The extract was made according to the method of Evans and Long ('21). Weight was recorded at 5-day intervals and every 10 days measurements of nose to anus and anus to tail tip (checked by total length) were made under deep ether anaesthesia. Injected animals received 1 cc. of extract daily. Weight, body length, tail length, and total length of the injected animals were graphed with like data from other members of the litter. Correlation shows the body length, tail length, total length, and weight of the untreated male castrate to be less than like those for both the control and the injected castrate. Injection of anterior hypophyseal extract increased the body length of the injected castrate to that of the

control and raised the weight of the injected castrate in most cases considerably above that of the control. Body weight in respect to body length is greater in the hypophyseal-treated castrate than in the control. Although the body length of the control and injected castrate is about the same, the total length of the injected castrate is greater because of the definitely greater response in tail length, giving a differential growth response of the body and tail.

—Author's Abstract.

Manganese toxæmia, with special reference to the effects of liver feeding. Charles (J. R.), *Brain* (Lond.), 1927, 50, 30-43.

Reports of seven cases of manganese poisoning are given. With the idea that the nervous phenomena are due to deficiency of a hepatic internal secretion treatment with liver was adopted, and some benefit was obtained in some of the cases.—A. T. C.

Crystalline insulin. Abel (J. J.), Gelling (E. M. K.), Rouiller (C. H.), Bell (T. K.) & Wintersteiner (O.), *J. Pharmacol. & Exper. Therap.* (Balt.), 1927, 31, 65.

The authors describe methods for preparing insulin in crystalline form, the technique of testing potency, and also many details of a highly technical and complicated nature for which the reader is referred to the original article. The percentage composition for air-dried material was found to be C, 49.91%; H, 7.16%; O, 25.58%; N, 14.41%; S, 2.94%; H₂O, 5.35%. It is suggested that the molecular weight is about 1000 and that the empirical formula for dehydrated material is C₄₅H₆₉O₁₄N₁₁S and for the air-dried product, either C₄₅H₆₉O₁₄N₁₁S. 3 H₂O or C₄₅H₇₅O₁₇N₁₁S. The crystals are about 0.01 mm. in diameter and fall into two crystallographic groups which suggest that the substance is dimorphous since there is no difference in chemical composition in the two types.—C. I. R.

Chemical composition of insulin, sulfur compounds. Boivin (A), *Compt. rend. Soc. de biol. (Par.)*, 1927, 96, 45-46; *Abst. Chem. Absts.*, 21, 1131-1132.

The major portion of sulfur of insulin may be split off as the H₂S by alkalis and heat. It is probable that the non-labile sulfur is present as impurities. The sample of insulin studied gave no reaction for SO₄, and on prolonged heating with HCl gave no H₂S.

A contrast of the chloride contents of corpuscles and plasma in pernicious anaemia and various other conditions. Cameron (A. T.) & Foster (Marion E.), *Canad. M. Ass. J. (Montreal)*, 1927, 17, 670-675.

Both plasma and corpuscle chlorides are below normal in dia-

betes mellitus, the degree of lowering being to some extent related to the severity of the condition. Balancing the metabolism with insulin tends to restore these values to normal.—A. T. C.

Diabetic lipaemia retinalis. With report of a case. Chase (Lillian A.), *Canad. M. Ass. J.* (Montreal), 1927, **17**, 197-204.

The case showed hyperlipemia, hyperglycemia, acidosis, and glycosuria. The two latter cleared up rapidly and the lipemia in 15 days on insulin treatment.—A. T. C.

Animal passage hypoglycaemia. Collip (J. B.), *Proc. Soc. Exper. Biol. & Med.* (N. Y.), 1927, **24**, 731-732.

The author is convinced that animal and plant insulin are similar and that the phenomenon of "animal passage hypoglycaemia," which he described as associated with the latter, is due to a contaminating organism.—J. C. D.

Insulin in dermatology. Darnet (J. J.), *Semana méd.* (Bs. Aires), 1927, **34**, 819; *Abst., J. Am. M. Ass.*, **88**, 2006.

In all cases of a chronic skin lesion, Darnet advises investigation of the blood sugar. If a high count is found, insulin should be tried. Even when the figures are normal, an induced hyperglycemia test may yield a different result. In more than 100 cases of eczema, furunculosis, psoriasis, arsenical erythroderma, ulcers of the leg, intertrigo and acne, insulin was used and proved curative in many. The dosage was rather high, occasionally as much as 100 units a day.

The influence of insulin on the treatment of surgical complications in diabetes mellitus. Foster (D. P.) & Davidson (E. C.), *Ann. Clin. M.* (Balt.), 1927, **5**, 639-655.

The results of surgical treatment in forty-eight patients with diabetes mellitus are tabulated. Preoperative and postoperative diets containing liberal calories and carbohydrate with insulin in quantity sufficient to control the blood sugar were found satisfactory. A high fluid intake was also found important. The most dangerous complications for the diabetic were found to be infection and gangrene. The danger of acidosis is very slight in patients operated on if time is available for adequate preparation. Ethylene is a suitable anaesthetic for the diabetic. Mortality rates have definitely become lower in the surgery of diabetics since the discovery of insulin.—Daniel P. Foster.

Insulin by innunction a failure. Harrison (G. A.), *Quart. J. Med.* (Oxford), 1927, **20**, 187-192.

The results of Telfer, Campbell, Macleod and McCormick, and

Wallgren with insulin inunctions suggest that this method of administration is effective in lowering blood sugar. Four observations were made upon human patients and two on rabbits. In two of the observations on the human patients 100 units of insulin in an almond oil base were rubbed into the skin. In the other cases 300 and 1,000 units were used. The rabbits received 100 units rubbed into the shaved abdomen. From his results the author feels that insulin inunctions are unsatisfactory and that there is no insulin absorbed through the intact human skin.—E. Larson.

Hypoglycemia in children. Herlitz (C. W.), *Hygiea* (Stockholm), 1927, 89, 329-335.

The insulin requirement fluctuates markedly during infections. It is often necessary to treble the amount of insulin given before. At times the normal dose may be resumed as soon as the temperature drops to normal. In other cases, large doses must be continued during convalescence. It is in such cases that insulin reactions are apt to develop. In children between one and five years of age, severe symptoms of hypoglycemia may come out of a clear sky. Thus a child of five, who was walking around, suddenly broke out in a sweat and was in a stupor within two minutes. Children may go through all stages of hypoglycemia without any characteristic alteration of the pulse. Paleness is perhaps the most pathognomonic symptom of an overdose of insulin. Insulin stupor and diabetic coma may be distinguished by the fact that the respirations are unchanged in insulin stupor. Children in coma require rather large doses of insulin. The author gave an 11-months-old child 112 units in 24 hours and 20 units per day for a long period afterwards. As a rule 30 to 70 units is sufficient to bring a child up to age five out of coma. The symptoms of hypoglycemia vary greatly in children, but they are always similar in the same child. At times it may take a child weeks to recover from the symptoms of an overdose of insulin. Epinephrin is of very little benefit in the cases of children with severe diabetes that suffer from hypoglycemia. Usually a bit of sugar promptly clears up the symptoms. In severe cases 5 to 10 cc. of 10% glucose should be given intravenously and may be followed by 100 to 150 cc. of the same solution hypodermically if necessary.—D. J. Glomset.

Islands of Langerhans and insulin after ligation of the veins that lead from the pancreas. Herxheimer (G.), *Klin. Wchnschr.* (Berl.), 1926, 5, 2299-2302; *Abst. Chem. Absts.*, 21, 956.

A complete ligation of the efferent vessels of the pancreas, in chickens, leads to a uniform atrophy of the organ, a tremendous enlargement of the islands of Langerhans, a hypoglucemia of such

severity that the animal becomes moribund and a five-fold increase in the insulin content of the pancreas.

The relationship of obesity to carbohydrate metabolism. John (H. J.), *Am. J. M. Sc. (Phila.)*, 1927, 173, 184.

The author reports twelve cases of obesity in which he studied the carbohydrate metabolism by means of glucose tolerance tests. The overweight in these cases ranged from 29 to 115 per cent. Glycosuria was present in two subjects, both diabetics. The fasting blood sugar was normal in eleven cases, among which four were cases of diabetes of varying degrees of severity, which means an incidence of a diabetic or prediabetic condition in 42 per cent. The author stresses the point that the carbohydrate tolerance should be investigated in all cases of obesity in order to give early protection to those who are diabetic or on way to diabetes.—Author's Abstract.

Insulin hypoglycemia in man. Klein (O.), *Med. Klin. (Berl. & Wien)*, 1927, 23, 312.

The author studied the fluctuations in the blood sugar following the injection of insulin. His observations can be summarized as follows: In diffuse, marked liver affections, the hypoglycemia is more marked, more lasting and appears sooner than in normals under the same condition. Such a hypoglycemia takes place even if carbohydrates are given by mouth in these cases—not appearing in normals. Such a hypoglycemia in liver affections is more prolonged and lasting when with or without the addition of carbohydrate a large quantity of water (1500 cc.) is given which also applies to normals. Chronically decomposed cardiac cases tend toward a more marked hypoglycemia following insulin, which the author explains as due to damaged liver function.—H. J. John.

The best times for blood sugar tests in diagnosis and treatment of diabetes. Lawrence (R. D.), *Practitioner (Lond.)*, 1927, 68, 114-124.

The author suggests that the blood sugar tests to determine whether there is diabetes be made before and one hour after a meal. He warns against the promiscuous use of the glucose meal, which may seriously injure a diabetic. He outlines the methods for ruling out renal glycosuria. In diabetics whose diet is satisfactory, the blood sugar should not exceed .18% to .16% one to two hours after a meal. In patients receiving insulin the maximum dose of insulin should be given in the morning and the sugar test made about noon.—J. C. D.

The influence of insulin on the utilization of the carbohydrates by the non-diabetic organism. [Ueber den Einfluss des Insulins auf

die Kohlenhydratverwertung im nichtdiabetischen Organismus. (Ein Beitrag zur Frage der Mastkuren mit Insulin).] Lublin (A.), Arch. f. exper. Path. u. Pharmacol. (Leipz.), 1926, 115, 101.

In an investigation of the much disputed effect of insulin on carbohydrate metabolism in the non-diabetic, experiments were carried out with Benedict's universal respiration apparatus. The author was able to prove that insulin is capable of increasing the formation of fat out of carbohydrates as assumed by Falta. In preliminary experiments the amount of carbohydrates (glucose or levulose by stomach) that just sufficed to bring the respiratory quotient to unity was determined. Then on the following day, under exactly similar conditions, the administration of the carbohydrate was repeated but with insulin given in addition. Under these conditions the R. Q. regularly surpassed unity.—Author's Abstract.

Secretion and the Golgi apparatus in the cells of the islets of Langerhans. Ludford (R. J.) & Cramer (W.), Proc. Roy. Soc. (Lond.), 1927, S. B. 101, 16-24.

By special technical methods that were proved to be adequate to determine degrees of secretory activity in the thyroid (see abstract, this issue), the authors studied the condition of the pancreas islet cells in rats and mice exposed to various environmental conditions. The cells were found to be highly variable, indicating different stages of activity, even in the same island, as normal findings. The most consistent trend of change was noted in pregnancy in which the Langerhans cells were especially active. A similar but less constant increase of activity was found after exposure to heat.—R. G. H.

On the effect of protein in the diet of patients suffering from diabetes mellitus. Lyall (A.), Quart. J. Med. (Oxford), 1927, 20, 115-122.

Five cases of moderately severe diabetics kept on protein diets were studied. Clinicians have attributed the deleterious effect of protein in diabetes to glucose derived from the protein molecule as well as its specific dynamic action. Petrón maintains that protein has an inherent deleterious effect. From his results the author concludes that the maintenance of nitrogen equilibrium on a low protein diet is desirable whenever possible. He also states that 2 gm. of protein per kgm. have no undesirable effect on sugar tolerance.—E. Larson.

The cholesterol content of the blood plasma as an index of progress in insulin-treated diabetics. Rabinowitch (I. M.), Canad. M. Ass. J. (Montreal), 1927, 17, 171-175.

Hyperglycemia indicates active diabetes, whether the individ-

ual does or does not show sugar in the urine. Insulin-treated patients cannot be said to have improved, as far as their pancreatic function is concerned, unless the blood sugar in the fasting state is normal. The clinical picture fails to be an index of progress in such cases. The lipid content of the blood is a better index of the course of the disease than is the blood sugar. An increased blood cholesterol is not compatible with favorable progress. Blood cholesterol determinations should be a routine procedure in the care of the diabetic, but other conditions affecting blood cholesterol should be borne in mind in interpretation.—A. T. C.

Insulin oedema. Rabinowitch (I. M.), *Canad. M. Ass. J.* (Montreal), 1927, 17, 685-687.

Insulin oedema may at times be harmful, in view of Joslin's suggestion that it may be a factor in the production of the anuria which develops during coma. Two cases are reported, in which polyuria and loss of weight followed discontinuance of insulin, and disappeared when insulin treatment was resumed.—A. T. C.

Activity of insulin and dysfunction of endocrine glands. Sacharoff (G. P.) & Danenkiff (J. S.), *Rev. Française d'Endocrinol.* (Par.), 1926, 4, 416; *Abst., J. Am. M. Ass.*, 88, 2004.

Sacharoff and Danekiff's study tended to verify the influence of certain substances on the action of insulin on the blood sugar. Fasting rabbits were given an injection of insulin, followed soon by an injection of one of the substances tested. Small doses of calcium increased the action of insulin; large doses considerably decreased its action. Magnesium constantly reinforced the effect of insulin. The action of sodium, potassium and phosphate was analogous to that of calcium. Distilled water appeared to enhance the action of insulin. The results confirm Kraus' theory that electrolytes play an important role in hormonal activity. Diet, fatigue, possibly even the seasons influence the effect of the hormone. In addition, changes in ion reactions induced by lesions of an endocrine gland may influence the action of a hormone on the intact gland.

Diabetes in a child three years of age. Smith (R. P.), *Canad. M. Ass. J.* (Montreal), 1927, 17, 214.

Satisfactory results of insulin treatment are reported.—A. T. C.

The influence of insulin and glucose on the oxygen-use of surviving frog's spinal cord (Ueber den Einfluss von Insulin und Glucose auf den Sauerstoffverbrauch des überlebenden Froschrückenmarks). Wolf (H. J.), *Arch. f. d. ges. Physiol.* (Berl.), 1927, 216, 322-336.

Insulin alone has no influence on the respiration of the spinal

cord of the summer frog; it does have a slight influence on that of the winter frog. Glucose addition alone has no influence on the normal cord, but on a mechanically damaged cord it frequently produces an increased oxygen consumption of short duration. Insulin in glucose solution produces an increased consumption of long duration. Too large insulin doses are without action or inhibit respiration.—A. T. C.

The relation of parathyroidectomy to pregnancy, lactation, and the growth of offspring in albino rats. Chandler (S. B.), *Anat. Record* (Phila.), 1927, 35, 7.

The parathyroid glands were removed from albino rats between the ages of 75 and 100 days. The animals were given from 2 to 3 weeks to recover from the effects of the operation and then mated with both normal and parathyroidectomized animals. A standard diet was used, with a liberal supply of meat every other day. Ten litters were secured. One female died 23 days after mating. She had 7 fetuses near term. The offspring of 4 other females died soon after birth or were eaten. The mothers apparently were unable to care for their young in these 4 cases. The weight of many of the offspring at birth was a little less than the normal, being about 4 grams in most litters. Growth was very much retarded in some litters or individuals, but if the young animals survived the lactation period, normal weight was usually attained in less than one week after weaning.—Author's Abstract.

The healing of fractures in parathyroidectomized albino rats. Chandler (S. B.), *Anat. Record* (Phila.), 1927, 35, 7.

The parathyroid glands were removed from a series of albino rats. One bone of a fore limb was fractured at the time of the operation and the fracture region studied histologically at 10, 14 and 21 days after operation. The age of the animals used ranged from 55 to 90 days. Litter mates were used as controls. Calcium determinations showed about 10 mgm. per 100 cc. of blood plasma in the control and about 5 mgm. in the experimental animals. No significant differences in healing were found in the two groups.

—Author's Abstract.

Effect of intraperitoneal magnesium sulphate on parathyroidectomized rats. Jung (F. T.) & Cook (F.), *Proc. Soc. Exper. Biol. & Med.* (N. Y.), 1927, 24, 586-587.

A 1% solution of the crystalline salt of magnesium sulphate injected intraperitoneally, 5 cc. for a 150 gram rat, will prevent the rat's dying of tetany following parathyroidectomy. Injections are begun 12 hours after operation and given daily. The rat is

immobilized for a time by the curare-like action of the drug, but recovers within an hour.—J. C. D.

On the increase of methyl-guanidine in the blood after parathyroidectomy. Paton (D. N.) & Sharpe (J. S.), *Quart. Exper. Physiol. (Lond.)*, 1926, **10**, 57-59; *Abst., Biol. Absts.*, **1**, 257-258.

Examination of blood taken from dogs before and after thyroparathyroidectomy showed a larger yield of crystals, resembling methyl-guanidine picrate in appearance and melting point, from blood taken during tetany than from normal blood. These results confirm the observations of Burns and Sharpe that there is a marked increase in methyl-guanidine in blood during parathyroid tetany.

Observation on the skeleton of the progeny of parathyroidectomized albino rats. Strong (R. M.), *Anat. Record (Phila.)*, 1927, **35**, 25-26.

Female albino rats which had their parathyroid glands entirely removed were mated with normal males and with males that had undergone the same operation. No difference was observed in the skeletons of their progeny at birth as compared with the offspring of normal rats of the same age. Evidence was found, however, of changes occurring during lactation.—Author's Abstract.

The effect of thyroidectomy and thyroid feeding on the cardiac output. Blalock (A.) & Harrison (T. R.), *Surg. Gynec. & Obst.* (Chicago), 1927, **44**, 617-626.

Dogs were used as experimental animals. The cardiac output is increased in hyperthyroidism and decreased in hypothyroidism. The change in cardiac output is usually somewhat greater than the change in metabolic rate. The administration of iodine (Lugol's solution) to animals receiving thyroid is followed by a marked decrease in cardiac output as well as in metabolic rate. This decrease continues for from 6 to 10 days, after which the cardiac output and metabolic rate increase rapidly. Both cardiac output and metabolic rate remain elevated for two months or longer after cessation of thyroid feeding, the former returning to normal first. Digitalis has less effect in decreasing cardiac output of hyperthyroidized dogs than of normal animals. Thyroid extract should be used with caution in myxoedematous patients presenting evidence of cardiac weakness, and withheld when cardiac decompensation supervenes. Iodine therapy is valuable for a time in hyperthyroid patients, especially when they have pronounced cardiac symptoms, but the prolonged administration of iodine is probably useless. Administration of digitalis is indicated in hyperthyroidism.—A. T. C.

Heredity in simple goitre. Brain (W. R.), *Quart. J. Med. (Oxford)*, 1927, **20**, 303-313.

A series of 6 families is reported, including among them 26 cases of simple goitre. In 2 of these families cases occurred in 4 successive generations. A second series of 5 families is reported, containing 12 cases of simple goitre associated with congenital deaf-mutism. Evidence is brought forward in support of the view that hereditary predisposition is a factor in the etiology of simple goitre in some cases. The inheritance of goitre is considered in relation to Mendelian laws. It is concluded that simple goitre may be the manifestation of more than one abnormal hereditary factor, two of which can be distinguished by their behavior in transmission.

—Author's Summary.

Tuberculosis of thyroid. Collier (F. A.) & Huggins (C. B.), *Ann. Surg. (Phila.)*, 1926, **84**, 804.

A report of five cases of tuberculosis of the thyroid gland. All the patients were women. In one case caseating tuberculosis and in two cases miliary tuberculosis were associated with adenomatous goitre. In the other two cases miliary tuberculosis was found in exophthalmic goitres. From their study the authors conclude that the view that tuberculosis stimulates the thyroid gland to an abnormal activity is untenable. To the end of the article is appended a brief summary of case reports found in the literature.—J. P. S.

Fever, infections and the thyroid-adrenal apparatus. Cramer (W.), *Brit. J. Exper. Path. (Lond.)*, 1926, **7**, 95-110; *Abst., Biol. Absts.* **1**, 272.

The author reviews evidence for the regulation of body temperature by the thyroid and the adrenal. He cites 2 new cases and reviews others in which patients having a high fever unaccounted for by bacterial infections were found (post-mortem) to have had adrenal hemorrhage. Histological evidence is given of similar appearance of the thyroids of rats injected with tetrahydronaphthylamin and human thyroids after severe pyrexia due to bacterial infection. The similarity between aseptic and septic fevers is pointed out and some therapeutic applications of the conception of the thyroid-adrenal apparatus as a controller of body temperature are discussed.

On cellular activity and cellular structure as studied in the thyroid gland. Cramer (W.) & Ludford (R. J.), *J. Physiol. (Lond.)*, 1926, **61**, 398-408; *Abst., Biol. Absts.* **1**, 272.

A clear relationship was demonstrable between the functional state of the gland and the mitochondria. In resting glands the mitochondria are barely visible; in active glands they are greatly

enlarged. The condition of the mitochondria is therefore a criterion for the functional state of the gland, and may, as Goetsch suggested, be useful in studying pathological conditions of the thyroid. The Golgi apparatus shows the same changes observed in the other gland cells: a simple, contracted form in the resting cell and an enlarged, convoluted form during activity, followed by disintegration into granules. The mitochondria, it is suggested, represent a mechanism by which the cell can produce great variations in surface energy within the cytoplasm. On the basis of accepted views such variations must be accompanied by changes in the distribution of the lipoids within the cytoplasm and the cell membrane. These changes, in turn, would affect the permeability of the cell.

A system of microscopic tubules in the thyroid gland. Fitzgerald (R. R.), *Canad. M. Ass. J. (Montreal)*, 1927, **17**, 542-543.

The presence of a system of microscopic capillaries in the thyroid is shown, confirming the work of Williamson and Pearse. In the colloid-storage phase of the normal gland they are drawn out to minute, hair-like lines, almost invisible. In the resting phase they appear as thick, branching and communicating lines, occupying a position near the center of the epithelial column. In the active secretory phase they appear as almost transparent tubules filled with deeply chromatic coarse granules. Similar structures are found in both exophthalmic goiter and "fetal adenomas."—A. T. C.

Movements of the empty crop of the fowl in acute hyperthyroidism (*Bewegungen des leeren Kropfes der Hühner bei akuter Hyperthyreose*). Lieberfarb (A. S.), *Arch. f. d. ges. Physiol. (Berl.)*, 1927, **216**, 437-447.

The movements of the fasting bird's crop are spontaneous, consisting of irregular periods of activity and rest, the rest periods being somewhat longer. In acute hyperthyroidism, produced by feeding a single heavy dose of dessicated thyroid, the time of action is increased relatively, and may continue uninterruptedly for two hours. The rhythm of contraction is accelerated, and the amplitude weakened and irregular. During the rest period frequent single contractions occur. After 14 to 16 days return to normal commences and is complete between 4 and 6 weeks.—A. T. C.

Studies on the antagonism between the thyroid gland and the pancreas (*Etude sur l'antagonisme entre la glande thyroïde et le pancreas*). Lundberg (E.), *Acta Med. Scand (Stockholm)*, 1926, **64**, 470-495.

On account of successful therapeutic attempts with insulin in cases of Morbus Basedowi, the fact that axolotl metamorphosis is produced only by thyroxin has been utilized by the author in order to investigate experimentally whether such effect of thyroxin can

be inhibited by insulin. Axolotls were used in the experiments, twenty-five of which were control animals. The insulin doses varied between 1 and 20 units every 4th or 5th day (altogether about 5 doses). All the animals treated with insulin died, but in none of these animals—without exception—was there, at the time of death, any sign of metamorphosis, while, on the other hand, such signs of definite nature were found in the control animals. The author, therefore, considers himself having proved an antagonism to exist between the pancreas and the thyroid which, in cases of hyperthyroidism, justifies the therapeutic administration of insulin.

—Author's Abstract.

The relation between the internal secretion of the thyroid gland and the cells of the sex glands (*Etudes sur le rapport entre les sécrétions internes de la glande thyroïde et celles de glandes sexuelles*). Lundberg (E.), *Acta Med. Scand.* (Stockholm), 1927, **65**, 499-520.

In order to investigate more closely whether ovarian or testicular extracts have any inhibiting effect upon the thyroid, the author in experiments with such extracts made use of the importance of thyroxin for the axolotl metamorphosis. The extracts used were "Hoffman-la Roche" preparations; "Ovoglandol" and "Testiglandol." The experiments were carried out with 18 experimental animals and 5 controls (half of each sex). The doses of the extracts varied between 20 and 200 cu. mm. every 4th or 5th day (5 times in all). It was shown that the "Testiglandol" had no inhibiting effect on thyroxin either in males or females. "Ovoglandol" had no effect in the males, but was found to inhibit the thyroxin effect to a considerable extent in the females.—Author's Abstract.

Latent postoperative tetany. Richter (H. M.) & Zimmerman (L. M.), *Surg. Gynec. & Obst.* (Chicago), 1927, **44**, 627-636.

Fourteen percent of the authors' thyroidectomies showed latent tetany. In most cases it cannot be detected unless objective examination for the signs is made. It may become manifest during pregnancy, menstruation, lactation, or the course of infectious diseases. It often occurs without demonstrable change in blood calcium level, appearing to indicate that fall of blood calcium is an associated and not necessarily an early phenomenon, rather than a cause. Tetany may be controlled by changing the intestinal flora to an aciduric type and by administration of calcium by mouth. Collip's extract should be used when the clinical manifestations do not disappear within a short interval.—A. T. C.

Effect of experimental hyperthyroidism upon plumage [*Dystrophies et dyschromies du système pileux dans le goître exophtalmique et hyperthyroïdisme expérimental (avec présentation d'animal en*

expérience)]. Sainton (P.) & Peynet (J.), Bull. et mem. Soc. med. d. Hôp. de Par., 1926, 42, 493-496; Abst., Biol. Absts, 1, 276.

The authors confirmed the observations of Zavadovsky. Administration of thyroid extract daily to an adult black hen resulted in the whitening and falling out of the feathers in certain areas. There was also rapid loss of weight, cessation of egg-laying, rise of temperature, increased excitability, and changes in the comb.

Internal secretion and pregnancy (Zur Frage: Innere Sekretion und Schwangerschaft). Schütz (F.), Arch. f. d. ges. Physiol. (Berl.), 1927, 216, 341-352.

Thyroidectomized rabbits show less frequent and irregular rut than normal. Labor weakness is shown, and the young are born at considerable intervals of time. The young show premature ossification of the epiphyses. Thyroidectomized rats always abort, and generally die during abortion. The number of foetuses is reduced.

—A. T. C.

Studies of hyperthyroidism. III. Bile pigment production and erythrocyte destruction in thyroid-treated amphibian larvae. Speidel, (C. C.), J. Exper. M. (N. Y.), 1926, 43, 703-712; Abst., Biol. Absts., 1, 276.

Experimental hyperthyroidism in urodele larvae (*Amblystoma*) and anuran larvae (*Rana*, *Bufo* and *Hyla*) is accompanied by definite changes in bile color. The normal pale green or pale yellow-green color of the full gall bladder changes progressively after thyroid administration to brighter green, emerald green, and finally very dark green. In several hundred observations no exceptions were noted. Biliverdin (and its derivatives) is elaborated from hemoglobin. Thyroid administration increases the rate of erythrocyte destruction, and thus the output of bile pigment. Other minor factors are mentioned which may modify the color of the bile. Erythrocyte destruction occurs largely by enucleation, cytoplasmic segmentation, and fragmentation, and is probably widespread. Many fragments and senile red cells collect in the liver. During later stages of thyroid treatment the macrophages become conspicuously active and are especially abundant in the liver, gut and gills. In addition to the hemoglobin eliminated after transformation into bile pigment, some is transported by macrophages through the gut lining, and to a less extent through the involuting gill epithelium, and thus eliminated from the body.

Studies of hyperthyroidism. IV. The behavior of the epidermal mitochondria and the pigment in frog tadpoles under conditions of thyroid accelerated metamorphosis and of regeneration following wound infliction. Speidel (C. C.), Morphol. & Physiol. (Phila.), 1926, 43, 57-79.

In the epidermal cells of green-frog tadpoles (*Rana clamitans*) there are present coarse, conspicuous mitochondrial threads. In the dorsal body regions, epidermal cells of the middle layers also contain pigment granules, grouped in crescentic masses in the distal portions of the cells. Administration of thyroid extract results in permanent disappearance of the mitochondrial threads and disappearance to a large extent of the epidermal pigment granules. Processes of cellular dedifferentiation and proliferation occur rapidly over widespread areas, the mitochondria undergoing intracellular resorption. A new type of epidermis is developed containing many cutaneous glands, adapted for the approaching terrestrial life. Wound infliction induces similar processes of cellular dedifferentiation and proliferation in the epidermis in the immediate vicinity of the wound. Cells in this region lose their mitochondrial threads by intracellular resorption, and there is also some disappearance of pigment granules. The new epidermal cells in the early stages of regeneration produce neither mitochondrial threads nor pigment. This condition is not permanent, however, and in the later stages the larval characteristics appear again, both mitochondrial threads and pigment being redifferentiated. In the hyperthyroid animals there is also a significant mobilization of mesenchymal chromatophores, correlated to some extent with the loss of epidermal pigment. The significance of epidermal changes is discussed with reference to cutaneous abnormalities associated with hyperthyroid and hypothyroid conditions.—Author's Abst.

Sporadic cretinism. Thoemes (F.), *Jahr. f. Kinderh.* (Leipz.), 1925, 110-167; Abst., *Child Development Abst.*, 1, 17-18.

By the term cretinism is understood the end-effect of a chronic disease characterized by dwarfism, idiocy, deafness, and goiter. However, there are many transitions from this extreme to the half-cretin and the cretinoid toward the normal. Endemic cretinism and thyroid disease are commonly associated. Sporadic cretinism, first described in 1870 by Hilton Fagge, was considered an athyreosis and since his time all forms of congenital and infantile myxedema have been considered under the head of sporadic cretinism, especially by those men who consider endemic cretinism as a pure athyreosis. Scholz considers infantile myxedema and sporadic and endemic cretinism as distinct. Infantile myxedema does not occur in goiter areas, and the characteristic changes of the skin seen in this condition are not seen in cretins. Myxedema clears up promptly on thyroid treatment; this is of great diagnostic importance. A case of sporadic cretinism is described in which dwarfism with overweight in proportion to height, cretinoid facies, normal skin, dry hair, pot belly, deafness and dumbness, normal sugar tolerance, as well as normal reaction to atropine, thyroid medication and epinephrine were the important observations along with

lymphocytosis and eosinophilia in the blood. Myxedema, lack of perspiration, obstipation, lowered body temperature, increased tolerance for sugar, atropine, and epinephrine and late appearance of the bone nuclei were not present. There was also a strong susceptibility to thyroid extract, showing that the case was not an athyreosis. Theomes considers the case more closely allied to endemic cretinism than to congenital myxedema.

Indications for thyroidectomy and late results from the operation.

Troell (A.), *Hygiea* (Stockholm), 1927, **89**, 225-311.

The author discussed 337 cases of goiter which he had operated upon. Of these, 193 were toxic, 125 were of the exophthalmic type, and 68 were toxic adenomas. Among the non-toxic there were four carcinomas and two adenomas. The mean value of the basal metabolic rate in the exophthalmic type was plus 55%, highest pre-operative rate plus 135. The highest rate in the toxic adenomas was plus 34. The basal rate was considerably reduced by pre-operative treatment with Lugol's solution, etc. In his experience, operation should always be done when the rate is receding. Patients around sixty do not stand the operation well. The operative mortality was 6.7%. The last three years it was 3.3%, due to better pre-operative care. On being discharged from the hospital nearly $\frac{4}{5}$ of the exophthalmic and $\frac{3}{4}$ of the toxic adenoma subjects had a basal rate of between plus 20 and minus 20 of the ultimate result, i. e., after from one to seven years after operation as known for 131 cases of toxic goiter. About 85% of these have been economically restored, 9% have had recurrences. Half of these were made well by a second operation. Troell thinks Lugol's solution has been of great benefit.

—D. J. Glomset.

The fixing of thyroxine in the organism of hyperthyroidized mammals (*Zur Frage der Feststellung von Thyroxin in Organismus hyperthyreoidisierter Säugetiere*). Zavadovsky (B.) & Asimoff (G.), *Arch. f. d. ges. Physiol.* (Berl.), 1927, **216**, 65-81.

Using the axolotl as test animal it is proved that the internal secretion of the thyroid may be completely taken up by the blood, liver, and kidneys, of hyperthyroidized mammals. In such animals the liver acts as a barrier, while to a slighter extent the kidney removes thyroxin. Thyroxin can be demonstrated in blood serum. The best time for testing is 5 hours after administration of the preparation. After 24 hours little or nothing is detected.—A. T. C.

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HEMOCHROMATOSIS. A REPORT OF THREE CASES
WITH RESULTS OF INSULIN THERAPY IN
ONE CASE*

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INTRODUCTION

Hemochromatosis is a rather rare disease characterized by deposition of pigment in the skin and various organs, cirrhosis of the liver, and often progressive sclerosis of the pancreas with severe diabetes mellitus. The first clinical description of the disease was published by Hanot and Chauffard in 1882. The name "hemochromatosis" was given to it by von Recklinghausen, who found that the pigmentation of the various organs in this condition was due to two pigments, hemosiderin and hemofuscin, of which the first is iron containing.

*Read at the Eleventh Annual Meeting of the Association for the Study of Internal Secretions, Washington, D. C., May 17, 1927.

The comparative rarity of hemochromatosis is shown by the fact that only three cases of it occurred in over 60,000 admissions to the University of California Hospital, and but the same number of cases was found among 106,000 medical admissions to the Johns Hopkins Hospital. Seventy-five cases of hemochromatosis were described in the literature up to 1918, and since that time fifty-one new cases have been reported. The disease attacks males mostly, as only five authenticated typical cases and one very early case in the female have been described. Hemochromatosis usually occurs between the ages of forty and fifty, but patients as young as twenty-eight and as old as seventy-three have been afflicted. Alcoholism, gastrointestinal disturbances and chronic copper poisoning are named by various authors as predisposing causes.

CASE HISTORIES

The three cases described here represent, by a fortunate coincidence, the three clinical types of hemochromatosis.

The first case is one of simple hemochromatosis without diabetes and, in addition, displays a rare condition, namely, primary carcinoma of the liver, which is found in a considerable proportion of cases with this disease. The second case, while having a perfectly typical pigment sclerosis of the pancreas with severe diabetes and cirrhosis of the liver, shows no increased pigmentation of the skin. The third case, which is still being studied, presents all three clinical features of the disease, diabetes, cirrhosis of the liver, and pigmentation of the skin, to a remarkable degree and also shows sexual hypoplasia. The special interest of the last case lies in the use of insulin therapy and its bearing on the prognosis of hemochromatosis.

CASE REPORTS

CASE No. 1. Hospital No. 9213. Simple hemochromatosis without diabetes. Primary carcinoma of the liver.

J. S., Scotch-American, aged 67, married, was admitted to the University of California Hospital on May 10, 1915, with a complaint of epigastric pain and swelling of the abdomen. He died on May 21, 1915, from a gastric hemorrhage.

FAMILY HISTORY includes nothing relevant.

PAST HISTORY.—The patient was born in California, but between the ages of 15 and 25 his profession as a jockey took him to Australia, New Zealand, France, England, Ireland and Southern Russia.

Since then he lived in every part of the United States where there are race tracks. In his later years he became a horse keeper. The patient was married and had three children. Measles in youth and right-sided pleurisy at the age of 64 are the only diseases recalled by the patient aside from several broken bones and many hard falls during his work around horses. He had gonorrhea six times and a bubo at the age of 32. Lues is denied.

Systems.—Head: The patient has had profuse perspiration over the left forehead for years. His vision had become a little blurred during the month before entry.

Cardio-respiratory: There was dyspnea on exertion, but no edema.

Gastro-intestinal: The appetite was always very good, but the bowels constipated. He had many bilious attacks in his youth but absolutely no stomach trouble since then until the present illness. He had hemorrhoids for years, which bled occasionally.

Genito-urinary: No abnormalities were present.

Neuro-muscular: No significant findings were disclosed except for poor sleep recently.

Habits: The patient was a steady drinker of alcohol but rarely became intoxicated. He also used coffee and tobacco in moderation.

PRESENT ILLNESS.—The onset has dated fourteen months before entry, when a horse fell across the patient's abdomen. This accident caused no serious injury, but the patient had a sore feeling and tenderness in the mid-epigastrium since that time. This soreness persisted to entry and was worse immediately after meals, so that he was gradually taking less food. Six months ago he noticed a progressive swelling of the liver and tenderness over it. The increase in the size of the liver was very rapid during the last few weeks. Three weeks before entry his urine became dark (he showed jaundice but did not realize it). During the last week prior to entry he began to have lower abdominal colic radiating into the testicles and lasting from two to three hours, sharp pains in the precordia radiating to the left shoulder, and sharp darting pains through the sides of the abdomen. During the last month he lost three kgm. in weight and became weak. He has been troubled at times with hiccough and gaseous distention, but never had nausea, vomiting, hematemesis, melena or diarrhoea.

PHYSICAL EXAMINATION.—The patient was a small, poorly nourished and moderately jaundiced man. The skin of the face and hands was deeply tanned and had a peculiar slaty hue. The arms and legs were similarly discolored but to a less marked degree. The skin was dry except on the face, where it was moist. The lymphatics were normal except for a few palpable nodes in the right axilla and both groins. Dilated venules were present over the cheeks. The sclerae were icteric. The pupils were small and irregular, the left smaller than the right, both reacting to light. The mouth showed poor hygiene and the breath was foul. Some congestion of the pharynx was present.

The right chest was larger than the left and its lower part flared out, due to presence of a large liver. The base of the right lung was compressed; otherwise the lungs were negative.

The heart showed no abnormalities. The temporal and radial arteries showed sclerotic changes. The blood pressure was 130/90 mm.

The upper abdomen, especially on the right, was very prominent. The superficial and superior epigastric vein, the thoraco-epigastric vein, and the inguinal branches of the deep epigastric vein were markedly enlarged. There was tenderness in the epigastrium. The liver was greatly enlarged and extended to slightly below the level of the umbilicus on the right and a little above it on the left, where a hard and sharp liver edge was felt with a notch in the gall-bladder area. The surface of the liver was smooth. The spleen was also enlarged, its dullness 16 cm. long, and the splenic edge was felt at the costal margin. There was no ascites. There was a large scar from an old bubo in the right groin. The genitalia showed enlarged veins on the scrotum, especially marked on the right, and a left varicocele.

On rectal examination a few old external hemorrhoids, an indefinite roll of tissue high up in the left pelvis, and a large amount of bowel in the pelvis were found.

The extremities showed enlargement of the right internal saphenous vein. All reflexes were present.

LABORATORY FINDINGS.—*Blood:* May 10. Hemoglobin was 70%; erythrocytes, 5,040,000 per c.mm.; leucocytes, 8,600 per c.mm., with a normal differential count. Smears showed pale erythrocytes and normal platelets. Platelets counted by Pratt's method showed 200,000 per c.mm. (within normal limits). Coagulation time by Lee and White's method was 9 minutes (normal, 5-8 min.). The Wassermann test was negative on two occasions. The serum was bile stained.

Liver function test: 25% of 500 mgm. of phenoltetrachlorophthalein given intravenously was excreted in the feces in 24 hours (normal, 30-40 per cent).

Urine: May 11 and 17—Chemical analysis showed bile++, urobilin+, slightest possible trace of albumin, no sugar. Microscopic examination showed a few leucocytes and rare granular casts.

Stools: May 11, 13 and 19. Some were solid and some were liquid (after catharsis), of a light brown to brown color. Chemical analysis showed the presence of urobilin and urobilinogen, but no frank or occult blood. Under the microscope no undigested food, particles of fat, ova, parasites or Oppler-Boas bacilli were seen.

Stomach contents: May 13, 45 minutes after a test meal showed a bile stained mucous fluid with food particles, having total acidity per cent of 6. There was no free hydrochloric acid. A test for lactic acid was slightly positive.

Duodenal contents: 10 cc. of cloudy yellowish fluid was obtained. Tests for lipase and trypsin were negative. A small amount of amylase was present.

X-rays: A gastro-intestinal series showed no abnormality except hyperperistalsis.

COURSE IN HOSPITAL.—While the patient was under observation, the pigmentation of the skin increased, especially on the hands and forearms. The left lobe of the liver became definitely larger. Tympany appeared over the splenic area and the edge of the spleen could no longer be felt. Signs of congestion appeared at the left base.

On the morning of May 20th, ten days after entry, the patient vomited 800 cc. of bright red blood. Following this he presented the picture of shock. The same night hematemesis recurred and the

patient passed large tarry stools. He failed gradually and died the following morning.

During his stay in the hospital, the patient's temperature was normal except for a single rise to 37.8° Centigrade. Pulse rate, respiration, blood pressure and fluid intake and output were not remarkable. He lost 0.4 kgm. in weight during the first week.

CLINICAL DIAGNOSIS.—Primary carcinoma of the liver with jaundice and splenic tumor. Pigmentation of the skin. Arterio-sclerosis. Varices of oesophagus, abdominal wall and scrotum. Gastric hemorrhage.

AUTOPSY, No. 15-57, was performed 4 hours after death, by Dr. J. Cooke.

Anatomical diagnosis: Hemochromatosis. Pigmentation of the skin, liver, pancreas and bronchial lymph nodes; cirrhosis of the liver; primary carcinoma of the liver invading the portal vein; oesophageal varices; hemorrhage into stomach and intestines; splenic tumor with chronic perisplenitis; chronic cholecystitis with cholelithiasis; chronic interstitial pancreatitis; chronic pulmonary tuberculosis (healed); pulmonary edema; chronic nephritis (slight); arterio-sclerosis; some atrophy of testicles.

Microscopical examination showed pigment deposits in the liver, spleen, pancreas, heart, kidneys, and lymph nodes, cirrhosis of the liver, chronic interstitial fibrosis of the pancreas, and adenocarcinoma of the liver with metastases to lymph nodes.

CASE NO. 2. Hospital No. 25,194. *Hemochromatosis without pigmentation of the skin.*

F. O'B., American, aged 40, single, came to the University of California Hospital on September 26, 1919, complaining of weakness and vomiting. He died on September 27, 1919, in diabetic coma.

FAMILY HISTORY was not relevant.

PAST HISTORY.—The patient was born in San Francisco and devoted himself to art. Between the ages of 23 and 33 he studied art all over the United States, and after that went to France and Italy for three years, returning after this to the place of his birth. He was well all his life and did not recall any diseases except a Neisserian infection three years before entry.

Gastro-intestinal: The patient never had any gastric or abdominal distress until the present illness.

Habits: Occasionally he drank alcohol.

PRESENT ILLNESS.—The patient had been losing weight for two to three years. Four days prior to entry he started vomiting and since that time had been unable to retain food or liquids. The vomitus was yellow in color and had a bitter taste. No other history was obtainable from the patient except that he had been mentally depressed since he was unjustly accused of starting a fire in the woods.

PHYSICAL EXAMINATION.—(By the intern.) The patient was an extremely emaciated man, looking older than his given age. He was not normal mentally. The skin showed no unusual pigmentation. There were enlarged axillary lymph nodes on both sides. The patient had very prominent features due to emaciation. The patient's breath had an odor of sour milk. His teeth were in poor condition

and the gingival margins showed retraction. The thyroid was barely palpable. All bones of the thorax were very prominent. The lungs were normal. The heart was somewhat enlarged to the left. The arch of the aorta was markedly widened and extended 8 cm. to the left in the third interspace. The first sound was loud, rough, and prolonged. The second sound was barely audible at the base. There was a suggestion of a diastolic murmur over the aortic area. The abdominal wall was thin and allowed the notched liver edge to be seen; also the outline of the colon across the abdomen. There was no tenderness. The liver was markedly enlarged, its edge being seen and felt 5 cm. below the right costal margin and 10 cm. below the xyphoid process. The spleen was not felt. All reflexes were present.

LABORATORY FINDINGS

Urine: Sept. 27, showed light color and specific gravity, 1.030. Chemical analysis showed sugar+++; acetone+++; diacetic acid+++; albumin+++. The sediment showed granular and hyaline casts.

Blood: Sept. 27. The plasma CO_2 tension of the venous blood was 30 per cent by volume.

Course in Hospital.—On the morning after entry the patient became comatose and his breath had the smell of acetone. At noon Cheyne-Stokes respiration was noted and an hour later he expired. During his stay in the hospital, his temperature was subnormal, ranging between 35.4° and 35.7° Centigrade. The pulse rate was 95 to 122 per minute and the respiratory rate, 16 to 25 per minute.

Clinical Impression (of the intern): The patient showed evidence of diabetes mellitus with coma and aortitis (probably luetic).

AUTOPSY.—No. 19-143, was performed within 4 hours after death by Dr. G. Y. Rusk.

Anatomical Diagnosis: Hemochromatosis; pigmentation of the liver, pancreas, spleen, mesenteric and aortic lymph nodes; perilobular cirrhosis of the liver; chronic fibrous pancreatitis; fibrosis of the mitral valve; general emaciation.

Microscopical examination showed pigment deposits in the liver, pancreas, lymph nodes, heart, kidneys, and adrenal glands; cirrhosis of the liver; and chronic interstitial fibrosis of the pancreas.

CASE NO. 3. Hospital No. 57,704. *Hemochromatosis. Sexual hypoplasia.*

D. O'L., Irish, aged 53, married, was admitted to the University of California Hospital on November 24, 1926, complaining of weakness, polydipsia, polyuria, and cramps in his legs. He was discharged as markedly improved on January 28, 1927, and is at present under observation in the Out-Patient Department.

FAMILY HISTORY.—Most of the members of the patient's family have had scant body hair. Otherwise the history was not relevant.

PAST HISTORY.—The patient was born in Ireland and worked on a farm until he was 27 years of age, when he came to San Francisco and did pick and shovel work laying gas pipes up to four years ago, when he became a night watchman. He claims to have had no childhood disease and has always been well, with the exception of a mild attack of influenza in 1918 and an occasional sore throat. His

right ankle was fractured a year ago and he was incapacitated for two months. He denied venereal infections. His marriage at the age of 39 resulted in three normal children.

Systems—Integument: The patient noticed a darkening of the skin over his legs one year ago.

Head: The patient has been quite deaf in both ears for the past 12 years and occasionally has tinnitus aurium. He has been treated for pyorrhoea and has had much dental work done.

Cardio-respiratory: There has been some edema of legs during the last three or four years.

Gastro-intestinal: The patient never had any symptoms referable to the gastro-intestinal tract except for occasional diarrhea.

Neuro-muscular: He has had occasional headaches and has suffered from cramps in his leg, coming on in bed, during the past eight or nine years. These became much worse during the month before entry. For the last three years he has felt cold.

Habits: The patient has been drinking considerable amounts of strong alcoholic beverages, especially before prohibition, when he used to drink a glass of whiskey every morning before breakfast. His beard has been scanty and he has shaved only twice a week.

PRESENT ILLNESS.—About a year ago the patient noticed darkening of the skin on his legs, but felt perfectly well until two months ago, when he first noticed extreme thirst. Drinking of large amounts of water was followed by marked polyuria and nocturia two to three times a night during the last two weeks. He noticed no increase in his appetite but an enumeration of the things he ate definitely indicates polyphagia. About six weeks ago the patient became aware of a rapidly increasing weakness and about the same time cramps in his legs, which he had for eight or nine years, became much worse. Approximately ten days before entry the patient began to feel mentally dull and drowsy. He grew steadily worse until his entry to the hospital. During the last six weeks he lost 13.5 kgm. in weight.

PHYSICAL EXAMINATION.—The patient was an emaciated man, looking older than his given age. His skin was dry and scaly. It showed a marked loss of weight and the subcutaneous fat felt granular. The legs showed a striking brown pigmentation which was also present over the back of his hands (see Fig. 1). The arms, face, and neck showed a peculiar grayish, slaty discoloration. The mucous membranes showed no abnormal pigmentation. The hair on the scalp was scant and the eyebrows were thin. Hair was totally absent on the chest and in the axillae. The pubic hair had a female distribution. One lymph node 1.5 x 1 cm. in size and several smaller lymph nodes were palpable in the right axilla, while large bunches of hard, 2 x 3 cm., discrete, lymph nodes, non-adherent to the skin, were felt in both groins. The eyes of the patient were watery. The pupils were small and irregular but reacted normally to light and accommodation. The fundi showed increased white lines on the arteries. The mouth showed poor hygiene and pyorrhea alveolaris. The patient was quite deaf. The ear drums were intact but showed marked retraction, especially on the left. The chest exhibited marked wasting and the right side was bulging anteriorly. The lungs were emphysematous. The heart was moderately enlarged to the left. All superficial arteries were hardened and showed pulsations which were very marked in the neck and arms. The blood pressure was 96/70.

The abdomen was distended and the abdominal wall was thin. Four engorged branches of the deep epigastric veins were seen on the lower abdomen. The liver was enormous in size and its shape and hard edge was felt at the level of the umbilicus from one flank to the other. The liver was not tender and presented a smooth surface. The spleen was not palpable, and tympany masked the area of splenic dulness. No ascites could be noted.

The genitalia were small. The foreskin was inflamed. On rectal examination an extremely small atrophic prostate was felt, the upper limits of which were easily reached. It was elastic throughout and the furrow was easily made out. The lateral sulci were very shallow. No hemorrhoids were found. The extremities showed early clubbing of the fingers with cyanotic finger nails. The second left was a "hammer toe." A few varicose veins were present in both legs.

LABORATORY FINDINGS.—Blood. Nov. 26. (1) *Formed elements of the blood:* Hemoglobin was 92% (Sahli); erythrocytes, 4,030,000 per c.mm.; leucocytes, 7,400 per c.mm., with a normal differential count. A smear showed nothing unusual in the appearance of erythrocytes and normal platelets.

Dec. 21. A reticulated erythrocyte count gave 1.5%. A fragility test for red blood cells showed beginning hemolysis at concentration of 0.4% and complete hemolysis at concentration of 0.3% NaCl.

Jan. 10. A platelet count by the indirect method gave 385,000 (normal between 400,000 and 600,000).

Jan. 14. Hemoglobin was 84% (Sahli); erythrocytes, 4,800,000; leucocytes, 8,600 with a normal differential count. Smears showed normal erythrocytes and platelets.

Jan. 25. Bleeding time was 3½ minutes; coagulation time, 7½ minutes.

Nov. 26. *Blood Wassermann* test was negative.

(2) *Blood Chemistry*—

Nov. 24. The *Blood Sugar* was 0.336. For later determinations see Table 3.

Dec. 8. The icteric index was 11.

Dec. 21. Blood serum CO₂; tension was 64.7 cc. bound as bicarbonate per 100 cc. of serum. N.P.N. was 33.6 mg.; urea N., 15.4 mg.; uric acid, 3.4 mg.; creatinin, 1 mg. per 100 cc. of blood.

Dec. 22. The icteric index was 8.1.

Jan. 6. The blood cholesterol was 156.7 mgm. per 100 cc.; plasma chlorides, 5.97 gm. per liter; serum protein, 6.5%.

Urine: Nov. 24. On entry, sugar was +++ acetone, +++ diacetic acid, none; urobilin, +; specific gravity, 1.016; albumen, none. On microscopic examination a few epithelial cells and amorphous debris were seen. For subsequent urine analyses from the diabetic viewpoint, see Table 3.

Dec. 26. Hemosiderin granules were demonstrated in tail-shaped cells presumably coming from the kidney pelvis after the sediment was treated according to the technic described by Pearl.

Jan. 15. Tests for melanin were negative.

Jan. 26. Hemosiderin was demonstrated in epithelial cells of the sediment by the method of Mallory and Wright (see Fig. 4).

Stools: Dec. 1. Nothing abnormal was presented except foul odor; urobilin was present.

Basal Metabolism Studies:

Dec. 1—19.6+.

Dec. 2—34.4+.

Dec. 7—19.5+.

Dec. 27—10.6+.

Jan. 13—7.5+.

Jan. 28—4.1+.

An electrocardiogram on Dec. 22 showed a P-R interval of 0.19 seconds, approaching partial A-V block; flattened T_1 , diphasic T_2 , indicating some myocardial abnormality.

Functional Tests:

I. *Fractional gastric analysis* on Nov. 30, following an Ewald test meal, was within normal limits.

II. *Rose-Bengal liver function test:*

Nov. 30. At the end of 8 minutes, 40% of the dye was found in the blood (normal 60%).

At the end of 16 minutes, reading not comparable.

Jan. 27. At the end of 8 minutes, 62% of the dye was found in the blood.

At the end of 16 minutes, 45% of the dye was found in the blood.

These findings indicate no impairment of dye excretion on the part of the liver.

III. *Renal function tests:*

A. *Mosenthal test*, Dec. 29, showed a fixation of the variation of specific gravity to 4 points (variation between 1.002 and 1.006). The day urine was twice the amount of the night urine.

B. *Phenosulphonephthalein test*, Dec. 30: 55% (35% and 20%) of the dye was excreted at the end of two hours.

IV. *Carbohydrate utilization tests:*

A. *Glucose tolerance test*, Jan. 14, after 80 gms. glucose by mouth:

Time	Blood Sugar	Sugar in Urine
Fasting	0.187	—0
½ hour	0.246	—0
1 hour	0.320	++
2 hours	0.396	+++

B. *Levulose tolerance test*, Jan. 29, after 100 gms. levulose by mouth.

Time	Blood Sugar	Sugar in Urine
Fasting	0.156	—0
½ hour	0.178	—0
1 hour	0.231	—0
2 hours	0.283	+

X-rays:

Nov. 27. *Chest plate:* Hilus shadows are increased. There is marked prominence of lung markings. The heart is hypertrophied. The arch is slightly widened and sclerotic.

Nov. 30. *Gastro-intestinal series:* The duodenal cap in the P. A. view suggests spasm; otherwise the findings are negative.

Dec. 3. *Barium enema* showed no abnormalities.

Biopsies:

Nov. 30. Two enlarged lymph nodes were removed from the left groin.

Nov. 30. A section of skin was taken out with a punch from the right leg.

Dec. 31. One enlarged lymph node was excised from right axilla.

Jan. 18. A section of skin was dissected out from the left leg.

PATHOLOGICAL REPORT by Dr. R. Millzner and Dr. E. I. Bartlett.

Gross Pathology: The specimen consists of two lymph nodes from the left groin, a small lymph node from the right axilla and two small fragments of skin from the leg. The lymph nodes all

measure approximately $1 \times 0.5 \times 0.5$ cm. Grossly they appear essentially negative.

Microscopic Pathology: Sections of all the tissues were stained for haemosiderin and haemofuscin. The sections of skin show haemosiderin granules present diffusely throughout the corium. The granules tend to accumulate in small clumps and masses immediately beneath the epidermis and about the blood vessels. Numerous granules are present about the coils and ducts of the sweat glands. A few are seen in the endothelial cells lining the smaller vessels and capillaries (see Fig. 2). The haemofuscin is present in rather coarse masses just beneath the epidermis. An occasional diffusely scattered granule is also seen (see Fig. 3).

Both the inguinal and axillary lymph nodes show the same pigment distribution, although the pigment is more abundant in the former. The haemosiderin appears chiefly as small scattered granules. These are most abundant in the hyperplastic endothelial cells lining the lymph sinusoids and in the reticulum immediately beneath the capsule. Small amounts are also present throughout the reticulum of the lymph node. Occasional haemosiderin granules are present in the endothelial cells lining the blood vessels (see Fig. 5). Haemofuscin is less abundant and forms relatively coarse granular masses. Most of the haemofuscin is scattered throughout the reticulum of the lymph node. Small amounts are present in the lining cells of the sinusoids and beneath the capsule (see Fig. 6).

COURSE IN HOSPITAL.—The patient came to the hospital in diabetic acidosis. The treatment of acidosis and subsequent treatment of diabetes is outlined in Table 3. On the day following admission the patient became alert mentally and felt much better. On the fourth day after entry the severe cramps in the legs which were one of his main complaints, went away. One week after entry the patient was put on 50 mgm. of ephedrine three times a day for the relief of hypotension, with a resulting increase of 10 to 12 mm. in his systolic blood pressure as long as the drug was given. Three weeks later the ephedrine was discontinued. At the end of the first month of observation the pigmentation of the patient's skin was definitely deepened, especially over the arms and neck. The size of the liver remained unchanged during his entire two months in the hospital. He steadily gained in strength.

The temperature was normal most of the time. On several occasions there was a slight fever and twice the temperature rose to 38.2° Centigrade. The pulse rate was between 70 and 90 per minute. Respirations were from 15 to 25 per minute. The fluid intake decreased from between 2 to 3.5 liters to from 1.5 to 2.5 liters per day in less than one month.

After discharge from the hospital the patient was referred to the Out-Patient Department and at the present writing has been seen there for three and one-half months at weekly intervals. For metabolic data during this period see Table 4. During this time the patient adhered to his diet and insulin dosage with one exception, when, for two weeks, he daily ate a small extra sandwich that was not covered by insulin. He reports a marked gain of strength and was permitted to resume his work as night watchman. Two weeks after starting work the patient developed some ankle edema at night on a cardiac basis. This edema disappeared in two weeks with small doses of digitalis. The patient's blood sugar level was found to be increased only once coincident with his dietary transgression, and his urine has remained sugar free except on the above mentioned occasion. The patient also gained 9.5 kgm. in weight.

Finally, the pigmentation of the skin over the legs, arms, neck and face has definitely become lighter since his discharge from the hospital.

CLINICAL DIAGNOSIS: Hemochromatosis; pigmentation of the skin; diabetes mellitus with acidosis; cirrhosis of the liver; inguinal and axillary lymphadenopathy; sexual hypoplasia; arterio-sclerosis; hypotension; chronic myocarditis with cardiac hypertrophy; pulmonary emphysema; pulmonary osteoarthropathy; catarrhal otosclerosis.

MICROSCOPIC DIAGNOSIS: Hemochromatosis with hemosiderin and hemofuscin deposits in the skin and lymph nodes.

DISCUSSION OF CASES ETIOLOGY AND PATHOGENESIS

The predisposing causes for hemochromatosis which have been advanced in the literature are alcoholism, gastro-intestinal disturbances, and chronic copper poisoning. The past history of the three cases reported here show that the use of alcohol is the only factor common to all. Moreover, in Cases No. 1 and No. 3, alcohol was taken habitually and in considerable amounts. No definite indications of chronic copper poisoning were discovered in any of the patients and their occupations as jockey, artist, and pick-and-shovel laborer, respectively, give one no reason to suspect intimate contact with this metal, unless it be through the medium of distilled liquors. As far as gastro-intestinal trouble is concerned, the absence of it in the patients under discussion, who were afflicted with such a chronic disease involving to a greater or lesser degree almost all organs of the body, is, indeed, unexpected.

Four theories as to the pathogenesis of hemochromatosis have been advanced. The first theory recognizes a primary disturbance of the iron metabolism of the body, resulting in a retention of iron and overloading of various organs with iron pigments. This deposition of pigments in the viscera and skin is held responsible for cirrhosis of these organs, especially the liver and pancreas, resulting clinically in diabetes mellitus, hypertrophic cirrhosis of the liver, and bronzing of the skin.

The second theory explains the flooding of the body with pigment on the basis of excessive hemolysis rather than a perverted iron metabolism. The third and fourth theories put forth diabetes mellitus and cirrhosis of the liver, respectively, as primary disturbances responsible for the clinical entity.

Data gained from study of our cases and having a bearing on the pathogenesis of hemochromatosis are in complete accord with the more or less generally accepted metabolic theory, while one or more of these cases stand in direct conflict with the other theories.

In the first place, in two cases where careful studies of the blood were made, the latter presented a perfectly normal picture and, in particular, no evidence of excessive hemolysis or increased activity on the part of the bone marrow was found. Furthermore, in one of our cases, diabetes was absent and in two of them cirrhosis of the liver, while present, seemed to be quite latent.

ONSET. The mode of onset and time elapsing between the first appearance of symptoms and admission of the patients to the hospital are of interest. In Case No. 1, which was complicated by primary carcinoma of the liver but did not have diabetes, a constant epigastric pain following an accident fourteen months prior to entry was the first symptom. Swelling and tenderness of the liver appeared eight months later, and during the last month before admission, weakness, loss of weight, and jaundice developed. In Case No. 2 only an incomplete history was obtained in which a loss of weight during the last two or three years was emphasized. This, in connection with the fact that the patient came to the hospital in diabetic acidosis which was shortly followed by coma, points to diabetes as the feature of the case which was probably the first to appear. Whether its onset was coincident with the loss of weight is open to question because the diabetes associated with hemochromatosis is usually of a severe nature and runs a rapid down-hill course. In Case No. 3 the disease was ushered in by an increase in pigmentation of the legs, which was noticed by the patient one year before entry. The classical symptoms of diabetes appeared with great vehemence two months before admission, at which time the patient already had acidosis.

CLINICAL PICTURE. It is convenient to discuss the clinical picture of hemochromatosis by the three main organs that are most conspicuously involved, the skin, the pancreas, and the liver, but one should not lose sight of the fact that pigment deposits, to a greater or lesser degree, are found in almost all



Fig. 1. Extensive brown pigmentation of legs in Case No. 3. Plate was made by Commercial Art Engraving Co., S. F., from colored print made by the "Direct color photo-process."

tissues of the body and may be accompanied by a corresponding degree of damage.

I. *Pigmentation of the Skin.* It is a very important feature of the disease from the point of view of clinical diagnosis, which is hard enough to make even in the presence of pigmentation. This is well shown, for instance, by the fact that only two out of seventeen cases of hemochromatosis reported by Mills from the Boston City Hospital were recognized during life. In our own series only the last case was diagnosed clinically. However, pigmentation is found in a majority of cases and frequently is very striking. Two types of pigmentation of the skin have been described, one a primary pigmentation which is due to deposits of hemosiderin and hemofuscin in the skin. When present, it lends to the skin a peculiar slaty hue in addition to a brown discoloration. In some cases there is also present what may be termed a "secondary" pigmentation due to increased amounts of melanin in the skin of patients in whom the adrenal glands show unusually heavy deposits of hemosiderin. These cases also show a low blood pressure and really are mild instances of Addison's disease on the basis of hemochromatosis. The mucous membranes in this disease are free from pigmentation save in a few instances in which, in all probability, the pigment seen in the mucosae is a part of the already mentioned secondary melanosis.

In Case No. 1 the skin of the face and hands was markedly bronzed, that of the arms and legs being affected to a lesser degree. The peculiar slaty hue of the skin was present and the mucosae showed no discoloration. Case No. 2 presented no abnormal pigmentation of the skin or mucosae.

Pigmentation of the skin is absent in a considerable proportion of undisputed cases of hemochromatosis. Some writers estimate it to be absent in as high as 50 per cent of cases, but this figure is too high. The reason for the failure of the pigments to be deposited in the skin in these cases is unknown. Dutournier in 1895 advanced the theory that pigmentation of the skin is absent in cases which run a very acute course, but this view is not borne out by a review of the literature. The explanation probably lies in a general variability of pigment deposits which may spare even the pancreas, producing cases

of so-called simple hemochromatosis, without diabetes. The absence of pigmentation of the skin has no great importance except in so far as diagnosis of the condition is made much more difficult.

In Case No. 3 darkening of the skin on the legs was first noticed by the patient a year before entry. At the time of admission his legs, and to a lesser degree the back of his hands, were of a dark brown color, while the skin of the face and arms exhibited the characteristic slaty discoloration (see Fig. 1). Two biopsies were made upon the skin of the legs and large amounts of pigment demonstrated by means of special stains. Hemosiderin in the form of small granules was present diffusely throughout the corium. In addition, small clumps of it tended to accumulate immediately beneath the epidermis, along the blood vessels, and about the coils and ducts of the sweat glands. A few were also seen in the endothelial cells of the smaller vessels (see Fig. 2). Hemofuscin, on the contrary, was present in rather large masses just under the epidermis. Only occasionally could one see some scattered granules of this pigment (see Fig. 3).

A most interesting feature of the pigmentation of the skin is its rapid progress in the two patients that showed it while under observation, and the astonishing fact of its regression in the second of these cases. In Case No. 1 a note regarding the deepening of the color of the skin was made eight days after admission. In Case No. 3 a definite increase in pigmentation was noted at the end of the first month of the patient's stay in the hospital, and a marked decrease in the intensity of this pigmentation observed after four months of insulin therapy.

II. *Diabetes mellitus and other derangements of pancreatic function.* Diabetes is the aspect of hemochromatosis which, if present, is usually the first to appear and to compel the patient to seek medical advice. It usually occurs in a severe form and in the pre-insulin days caused exitus lethalis through acidosis and coma on the average of within a year from the first manifestations of diabetes. Other functions of the pancreas are but rarely impaired, judging from the cases reported in the literature. Occasionally faulty fat digestion and attacks of epigastric pain are cited as evidence of pancreatic involvement.

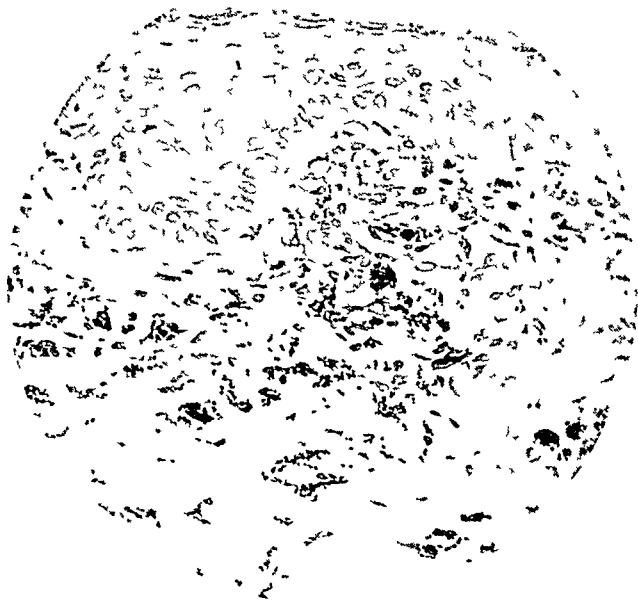


Fig 2 Section of skin in Case No 3 showing the diffuse distribution of small clumps of hemosiderin granules which are stained black by ammonium sulphide



Fig 3 Section of skin in Case No 3, demonstrating the occurrence of hemofuscin in large masses just beneath the epidermis. Hemofuscin stains brownish red with carmine

Our first case is classified as simple hemochromatosis without diabetes, since the urine was sugar free and there were no other diabetic symptoms in the history, though no blood sugar estimation or glucose tolerance test were performed as the case was diagnosed only at autopsy. As far as other tests of pancreatic function are concerned, the examination of the duodenal contents for ferments revealed the absence of trypsin and lipase, and the presence of small amounts of amylase. On the other hand, repeated examinations failed to show undigested food particles or defective fat splitting. Finally, epigastric pain was an early and prominent feature of the case.

In Case No. 2 diabetes is the dominant feature. The patient, who had been losing weight for two years, came to the hospital in a state of extreme weakness and emaciation and with an acetone breath after having vomited for four days. To complete the picture of diabetes with acidosis, his urine was light in color with a specific gravity of 1.030, and on chemical analysis gave strongly positive reactions for glucose, acetone, and diacetic acid. At the same time the plasma CO_2 tension of venous blood was 30 per cent by volume. True to form for the pre-insulin days, he became comatose on the day following admission, his breathing changed to the periodic type, and exitus followed shortly. No evidence pertaining to the external secretion of the pancreas was obtained.

Our third case also had as its presenting feature, diabetes. A history of extreme thirst, polyuria, polyphagia, weakness, and marked loss of weight during the two months before admission, coupled with a sudden onset of these symptoms and a definite drowsiness during the last ten days indicate the severity of the case. In addition, we have the blood sugar level, which was 0.336 per cent, and the urine, which was light in color, had a specific gravity of 1.016, and showed much glucose and considerable amounts of acetone. Moreover, the glucose tolerance test showed a typical, steadily rising diabetic curve that reached 0.396 per cent at the end of two hours, and demonstrates a high kidney threshold for glucose by the fact that there was no sugar in the urine with a blood sugar of 0.246 per cent thirty minutes after the ingestion of 80 gm. of glucose (1.7 gm. per kgm. of body weight). The results with insulin therapy are discussed

elsewhere. The basal metabolic rate in our patient was found to be 19.6 per cent plus and 34.4 per cent plus on two successive days shortly after entry. This is, according to DuBois, quite unusual for severe diabetes as in these cases the basal metabolic rate is lowered in proportion to the degree of emaciation, and in extreme cases may be 30 to 40 per cent below average. Such high figures for the basal metabolic rate in our case were the more unexpected because clinically the general appearance of the patient (dry skin, sparse body hair, thin eyebrows, etc.), was rather suggestive of hypothyroidism. An interesting speculation suggests itself in the light of the work of Foster and Woodrow, who describe a new pancreatic hormone that acts as an inhibitory agent for the anaerobic lactic acid formation in the muscles of the body. Since the basal metabolism of animals is, in large part, the recovery from the resting lactic acid production of their muscles, this new hormone might control the basal metabolism. In hemochromatosis where we have extensive sclerosis of the pancreas, the production of this hormone possibly can be reduced, as is that of insulin, so that the inhibition of resting lactic acid formation and recovery from it is removed with a resulting increase in the basal metabolism.

Duodenal contents were examined for ferments of the external secretion of the pancreas and found to contain trypsin and amylase. No undigested food particles or unsplit fats were found in the stools.

• III. *Cirrhosis of the liver.* Hepatic cirrhosis is invariably present in hemochromatosis. Clinically, it is usually shown by marked enlargement of the liver, but as a rule there are no symptoms of hepatic insufficiency or portal obstruction. The current explanation of this is that diabetic acidosis usually brings about a fatal termination, before cirrhosis has advanced far enough.

It is, therefore, of special interest to analyze the data having a bearing on liver dysfunction in our first case, in which no diabetes was present, though the presence of a primary carcinoma of the liver is apt to make some of the findings uncertain as to their origin.

The patient noticed swelling and tenderness of the liver six months before coming to the hospital. At entry the liver was

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It is, therefore, of special interest to analyze the data having a bearing on liver dysfunction in our first case, in which no diabetes was present, though the presence of a primary carcinoma of the liver is apt to make some of the findings uncertain as to their origin.

The patient noticed swelling and tenderness of the liver six months before coming to the hospital. At entry the liver was

found to be large and hard but its surface was smooth. During his stay in the hospital, a progressive enlargement of the left lobe of the liver was noted. So far the findings fit perfectly into the picture of uncomplicated hemochromatosis, especially the disproportionate enlargement of the left lobe of the liver which is very typical of this condition.

At the time of admission the patient had an hepatic facies and was moderately jaundiced. It is reasonable to suppose that the onset of jaundice dates back three weeks prior to entry since at that time the patient, who was not aware of the yellow discoloration of his sclerae and skin, noticed that his urine became dark. On the laboratory side we have bile stained serum and the presence of bile and urobilin in the urine. The jaundice did not perceptively deepen during the patient's sojourn in the hospital. Jaundice is very unusual in typical hemochromatosis but is present to a slight degree in about 30 per cent of cases of portal cirrhosis*, and it must be kept in mind that the absence of diabetes in this case has presumably permitted the hepatic cirrhosis to progress farther than is usual in hemochromatosis. On the other hand, 55 per cent of primary carcinomata of the liver show moderate icterus, so that its occurrence in our patient may be due to either condition, with the statistics being about 2 to 1 in favor of the malignancy as the cause for jaundice. Hemolytic jaundice is ruled out by normal blood findings.

In contrast to the usual latency of hepatic cirrhosis in hemochromatosis, the signs of portal obstruction in this case were pronounced but were accounted for at autopsy by invasion of the portal vein by the cancerous growth. The spleen was markedly enlarged. Also, a well developed compensatory circulation was established as shown by the enlargement of a number of subcutaneous veins, namely, the superficial epigastric, superior epigastric, thoraco-epigastric, inguinal branches of the deep epigastric, and scrotal veins. The fact that deeper venous anastomoses were also utilized for purposes of collateral circulation is proven by the fatal hemorrhage from esophageal varices in this case, indicating that the left coronary vein of the stomach was one of the important new channels.

* These figures are taken from Rolleston's report of 297 cases, quoted by Sir William Osler in "The Principles and Practice of Medicine."

Among other functions of the liver, the ability of this organ to excrete dyes was tested with phenoltetrachlorophthalein and was found to be impaired as only 25 per cent of the dye instead of the normal 30 to 40 per cent was recovered in the stools. The somewhat prolonged coagulation time of the blood was probably due to jaundice. The manufacture of bile was undisturbed, as shown by examination of the feces.

In Case No. 2 the hepatic cirrhosis was entirely latent. Its presence was revealed only by a considerably enlarged liver, the edge of which was felt in the mid-line 10 cm. below the xiphoid process. No function tests were carried out because the patient died in less than twenty-four hours after entry.

The clinical investigation of liver damage in Case No. 3 is of particular interest, first, because this is in every respect a classical case of hemochromatosis, and, second, because time and circumstances have permitted the application of all modern methods used for investigation of functional disturbances of the liver. Clinically, the patient had hepatic facies (prominence of the facial bones, a muddy complexion, dilated venules, especially over the nose, and watery eyes). The liver was greatly enlarged, hard and smooth. The only indication of portal obstruction was some enlargement of the superficial epigastric veins.

We now come to the consideration of the various laboratory tests throwing some light directly or indirectly on the functional status of the liver. Analysis of the feces showed that bile was manufactured by the liver and delivered into the intestine in sufficient quantities to insure normal digestion. At the same time, the presence of urobilin in the urine and the small but definite rise in the icteric index, even in the absence of clinical jaundice, indicated some biliary retention. The possibility that the increased amount of urobilin in the blood and urine was due to excessive hemolysis was refuted by normal blood findings. The red blood cells were of normal fragility and showed no increased bone marrow activity, as judged by the per cent of reticulated cells and the absence of stripping or immature forms. The platelets were also present in normal numbers.

A normal cholesterol content of the blood suggests that no serious injury had been suffered by the ability of the liver to eliminate this product through the bile channels.

We have reasons to believe that the blood sugar regulating mechanism of the liver had been markedly impaired in this case. Efforts to prove this point will be made in the discussion on insulin therapy. On the other hand, by comparing the glucose and levulose tolerance curves, the ability of the liver to handle levulose better than glucose was still present, at least to some degree (see Chart No. 1).

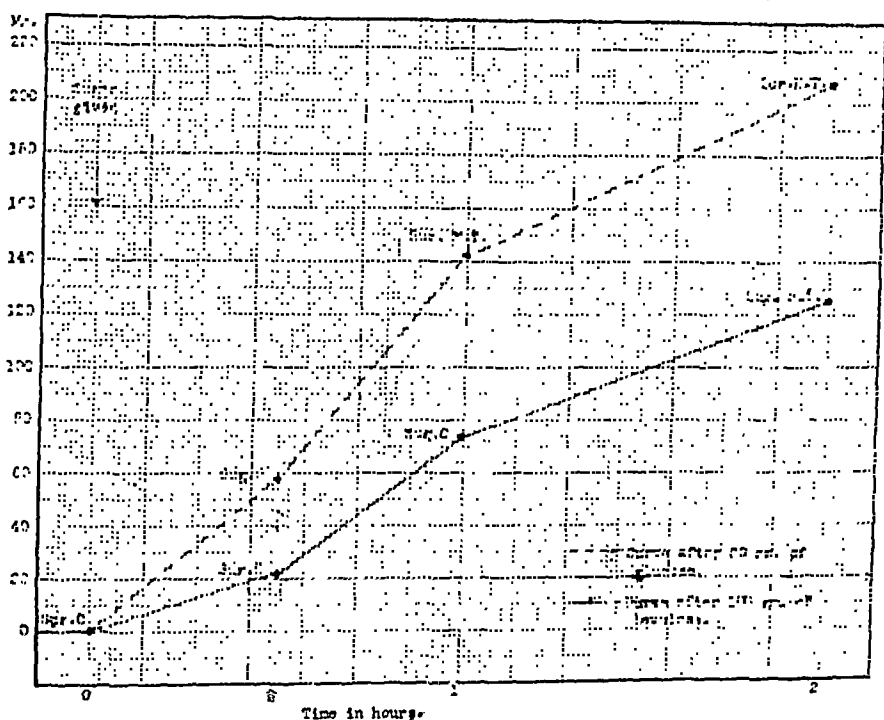


Chart I. Curves showing rise of blood sugar in Case No. 3 after ingestion of 80 gm. (1.7 gm. per kgm. of body weight) of glucose with a fasting sugar content of 187 mgm. per 100 cc. of blood and of 100 gm. (2 gm. per kgm. of body weight) of levulose with a fasting sugar content of 156 mgm. per 100 cc. of blood.

The dye excreting ability of the liver was tested by the Rose-Bengal method and found only slightly impaired. Fibrinogen production was sufficient, as shown by the normal bleeding and coagulation time. No abnormalities of liver activity in regard to protein metabolism and especially urea formation were found, as shown by the normal non-protein nitrogen partition of the blood. The level of serum proteins which is dependent on the liver was also found to be normal.

OTHER MANIFESTATIONS OF HEMOCHROMATOSIS. Among organs not yet discussed, the kidneys, the heart, the gastro-intes-

tinal tract, the adrenal glands, the gonads, and the lymphatic system, are the ones in which considerable pigment deposits have been found. It is of some interest, therefore, to look for possible clinical manifestations of such pigmentation in the organs mentioned above. In regard to the urinary system in our first case, we have a history of colicky pains in the lower abdomen radiating into the testicles. The urine showed a faint trace of albumen and, under the microscope, a few pus cells and rare granular casts were seen, but this was possibly due to jaundice. In the second case the only positive findings were a heavy trace of albumen and granular and hyaline cases in the urine, but the patient was in extremis and this very likely accounted for these findings. In our third case the urine betrayed no renal impairment but tailed cells presumably coming from the kidney pelvis were demonstrated with special staining methods to be filled with hemosiderin granules (see Fig. 4). The Mosenthal test



Fig. 4. Urine sediment in Case No. 3 with tail shaped cells from the kidney pelvis, many of which show hemosiderin granules after treatment with ammonium sulphide.

showed some fixation of specific gravity, probably accounted for by the presence of arteriosclerosis, while the phenolsulphonphthalein test and the non-protein nitrogen content of the blood were normal. So we can conclude that no marked impairment of renal function took place in any of the three cases even though

pigment deposits in the kidneys of the third case were demonstrated during life.

The cardio-vascular system also presented no findings which could be attributed directly to hemochromatosis. The first patient complained of dyspnea on exertion and sharp precordial pains for three weeks prior to entry. He also had some arteriosclerosis. The second patient had some enlargement of the heart and physical signs of aortitis. Our third patient also had some enlargement of the heart, arteriosclerosis of the arch and all peripheral arteries, and evidence of myocardial abnormality in the electrocardiogram.

The gastro-intestinal tract was studied from the clinical, laboratory and roentgenologic standpoint in Cases No. 1 and No. 3. Achlorhydria, with coincident gastric hyperperistalsis were the only positive findings in the first case. In our third case the gastro-intestinal tract was found to be normal in every way.

Several instances of marked pigment cirrhosis of the adrenal glands with the clinical picture of a mild Addison's disease in cases of hemochromatosis are described in the literature. Of the four principal symptoms of Addison's disease, weakness, low blood pressure, melanosis, and gastro-intestinal disturbances, only the first was present in Case No. 1 and Case No. 3, but in both instances could be accounted for on some other basis. Low blood pressure was found in our third case but no melanosis of the skin or the presence of melanin in the urine could be detected. We already have had occasion to comment on the freedom of our patients from gastro-intestinal symptoms. On the whole, we may conclude that no marked involvement of the adrenals was present in any of these cases although the weakness and hypotension in Case No. 3 could be regarded as possible early symptoms of hypoadrenalism.

Enlargement of the axillary and inguinal lymph nodes was found in Cases No. 1 and No. 3, and axillary lymphadenopathy alone in Case No. 2. In our third case two lymph nodes from the groin and one from the axilla were removed during life and the presence of both pigments in abundance was demonstrated by special staining. As in the skin, the hemosiderin appeared chiefly as small scattered granules which were most abundant in the hyperplastic endothelial cells lining the

lymph sinusoids and in the reticulum immediately under the capsule. Small amounts were also present throughout the lymph nodes, with occasional hemosiderin granules in the endothelial cells lining the blood vessels (see Fig. 5). Hemofuscin formed relatively large granular masses. More of the hemofuscin was scattered throughout the lymph nodes and small amounts of it were present in the lining cells of the sinusoids and beneath the capsule (see Fig. 6). Whether the pigment deposits are responsible for the lymphadenopathy is, of course, open to speculation.

Sexual hypoplasia was a feature of considerable interest in Cases No. 1 and No. 3. In the first case there was merely some atrophy of the testes which was found at necropsy. In Case No.

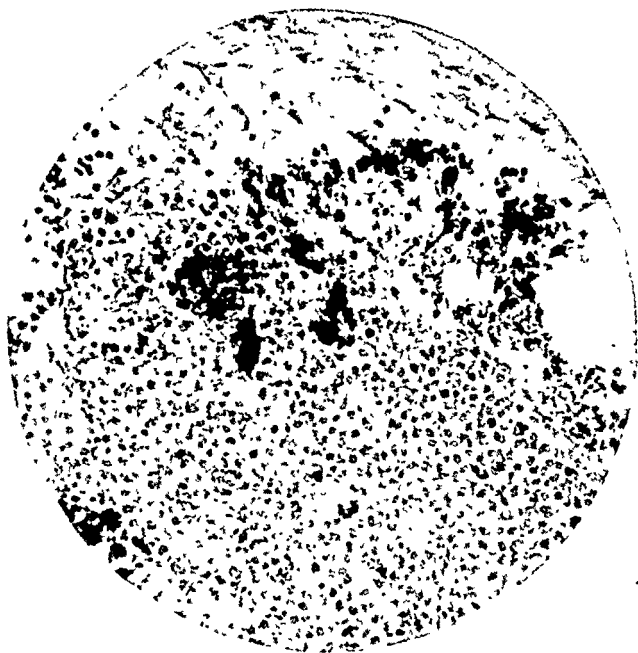


Fig. 5. Section of lymph node in Case No. 3 with accumulations of hemosiderin (showing in black) near a lymph sinus immediately under the capsule.

3 the patient gave a history of scant body hair in his family. He married at the age of 39 and had three children. Five months before entry he became impotent. The hair on his scalp and face was scant (he shaved only twice a week). The eyebrows were thin. His chest, axillae and extremities were totally devoid of hair. The pubic hair distribution was of the female type. The



Fig. 6. Section of lymph node in Case No. 3 showing brownish-red highly refractile granular masses of hemofuscin.

penis and testes were hypoplastic and the prostate very small and atrophic.

A review of the literature for the past ten years shows that among forty-four reported cases of hemochromatosis, sexual hypoplasia was met with in three cases. The salient features of these cases will be given now. Howard and Stevens report a case of hemochromatosis in a man aged 54 who had a light beard and moustache, and very sparse pubic hair. His genitalia and prostate were small, and the testicles were found to be atrophied on post-mortem examination. The man was the father of two children. Marsh describes a young man of 28 with hemochromatosis who gave the history of becoming impotent at the age of 17 though previously he was able to perform coitus. He had a feminine type of figure and only a few fine hairs on the face so that he never had to shave. There were only a few hairs in the axillae and his pubic hair was very sparse and of the female type. Both testes were small, as was the prostate. Finally, Hirsh, in giving the history of a case of hemochromatosis in a man aged 49 who had seven children, mentions very sparse soft hair on the chin with no further evidence of a beard, complete absence of hair from the axillae, and very little pubic hair of female distribution. The penis in this case was hypoplastic with a small left testicle and right sided cryptorchism.

In all four cases we have evidence of formerly normal sexual activity and, therefore, are justified in considering the sexual hypoplasia as acquired and probably due directly or indirectly to hemochromatosis.

Primary Carcinoma of the Liver. The relative frequency of primary carcinoma of the liver in hemochromatosis has been commented upon by several authors. Dumphy mentioned three cases of it in this condition between 1921 and 1924. Stewart, in 1922, collected five similar cases. Out of seventeen cases of hemochromatosis reported by Mills, three had primary carcinoma of the liver. Finally one of the three cases reported here also showed it. The current explanation of this frequency is that a continuous necrosis and regeneration of liver cells, which is known to occur in cirrhosis of hemochromatosis, finally leads to an escape of some cells beyond the agencies controlling normal growth with a resulting carcinoma. The incidence of primary

carcinoma of the liver is also high in simple portal cirrhosis. For example, Stewart found it in four out of a total of 149 cases of portal cirrhosis of the liver which came to necropsy, making 2.7 per cent. Including four other cases of primary carcinoma of the liver, there were altogether 8 cases in 6,000 autopsies at the Leeds General Infirmary, which gives a general incidence in this series of 0.13 per cent. The occurrence of this condition in cirrhosis of hemochromatosis is evidently even higher than in simple portal cirrhosis, as at least 12 cases have been reported in a total of 128 cases of this disease, or 9.1 per cent of all reported cases. The reason for this probably lies in the additional irritation produced by the presence of large amounts of pigment in the liver cells.

RESULTS OF INSULIN THERAPY IN HEMOCHROMATOSIS. Diabetes mellitus in hemochromatosis, with the exception of a few cases where it is absent, is always the factor which brings the patient to the doctor, occupies the foreground in the clinical picture as long as the disease lasts, and has so far proven to be lethal in all cases where it occurred. It is, therefore, of great interest to see what insulin therapy can do in hemochromatosis, in what way it will modify the clinical picture, and what influence it will have on the prognosis of the disease which heretofore has been so grave. The rarity of hemochromatosis still enhances the interest attached to its study because it is the investigation of the unusual in clinical medicine that is apt to throw new light on the fundamental principles of physiology involved in the functioning of the affected organs. A careful search of the literature yielded four cases of hemochromatosis in which insulin was given. The facts related to insulin therapy in these cases are briefly given below.

The first two cases were reported by F. Hirsh from the Von Jaksche Klinik in Prague. The first patient presented a typical picture of hemochromatosis and was in acidosis when admitted. He had had diabetic symptoms for six weeks previous to entry. The urine contained 3.6 per cent of glucose and gave a strongly positive reaction for acetone and diacetic acid. The blood sugar was 0.660 per cent. On entry the patient was given 50 units of "Pankreashormon 'Norgine'" intravenously and subcutaneously, and this was covered by a sufficient amount of levulose by

mouth. Later on the same day he received 150 units of insulin in small doses. On the second day the patient's urine contained 4 per cent of glucose and showed a trace of acetone, but no diacetic acid. At 9 a. m. he was given 50 units of insulin followed by 50 gm. of glucose and 50 gm. of levulose. The patient had been anuric since morning. On the morning of the third day the patient had a strong odor of acetone on his breath. He developed pulmonary edema and expired at 9:35 a. m. The second case of Hirsh was admitted in coma. The patient had hemochromatosis and was known to have had diabetes for three years. He received insulin on the outside for a short time but became worse six weeks prior to entry. On admission the patient was given 100 units of insulin (Wellcome) and 160 gm. of glucose. On the next day the patient's blood sugar was 0.561 per cent. *He was again given insulin in large doses, but died that afternoon.* The diagnosis of hemochromatosis in each case was confirmed by necropsy.

The report of the third case comes from Sanguinetti in Italy and contains a detailed account of treatment of a case of hemochromatosis with insulin over a period of eleven days. The diagnosis of diabetes was made in 1923. In spite of dietetic treatment the diabetes was progressing and in October, 1925, diacetic acid was found in the patient's urine. At the end of November, 1925, the patient came under the observation of Dr. Sanguinetti. Table No. 1 summarizes the important findings and follows the progress of the case as far as reported.

The author discusses his case from the angle of a dissociated action of insulin and comes to a negative conclusion.

The fourth case was reported by Hernandez and Benaros from Buenos Aires and contains a record of insulin therapy over a period of six weeks in a case of hemochromatosis. In this case symptoms of diabetes were first noticed, in a patient aged 37, in February, 1925. On March 23, 1925, the patient entered the hospital in a state of what the authors call "diabetic pre-coma" with drowsiness and Kussmaul breathing. The urine at entry gave strongly positive tests for glucose, acetone and diacetic acid. The patient was put on a non-weighed low caloric, low protein, high carbohydrate, and fat-free diet. The insulin dosage and urinary findings are given in Table No. 2. Appar-

ently no blood sugar determinations were made at any time.

The authors state that the patient fell into acidosis two more times. In the discussion of the case they emphasize the gravity of diabetes as evidenced by the rapid progress, marked tendency to acidosis and rebelliousness to dietetic and insulin treatment.

The outcome of the two German cases of hemochromatosis, when compared to the mortality per cent of simple diabetic coma treated with insulin, tends to indicate that in this condition the outlook is much less favorable when the stage of coma has been reached. However, more cases of this kind must be observed before definite conclusions can be drawn.

The Italian case, which as the output of 265 gm. of glucose in the urine on a total of 158 gm. of available carbohydrate in the diet shows, is one of so-called "total diabetes" and illustrates very well the severity of diabetes in hemochromatosis. From the standpoint of insulin therapy, this case demonstrates that, as far as the saving of life of the patient in acidosis of hemochromatosis is concerned, insulin is as effective as it is in that of simple diabetes. In the light of facts learned from the study of our own case, it is unfortunate that, as far as the report goes, no attempt was made to bring the blood sugar down to a normal level.

The Argentine case supports all conclusions which we felt justified in drawing from the Italian case in regard to diabetes in hemochromatosis: In addition there was a marked tendency to acidosis. It is true that the patient has not been on a weighed diet and no blood sugar determinations were made to serve as a guide in treatment, so that it is impossible for us to evaluate exactly this tendency to acidosis. But, assuming that the authors had considerable experience in the treatment of diabetes with insulin under these conditions, it seems safe to accept their statement as to the existence of such a tendency in the reported case.

Turning now to our own case, we see that the acidosis was easily controlled by 100 units of insulin and 800 cc. of orange juice containing 80 gm. of sugar divided into four doses (see Table No. 3). Six hours after entry the patient had an insulin reaction and his urine was free from sugar and acetone bodies. On the other hand, serious difficulties were encountered in trying

TABLE I

DIABETIC TABLE IN SANGUINETTI'S CASE OF HEMOCHROMATOSIS.

Days	Available Cbh. in the Diet	Units of Insulin	Glycosuria in gm. per 24 Hrs.	Acetone	Diacetic	Blood Sugar
1	158			++++	++++	
2	158		265	++++	++++	
3	179	80	160	++++	++	0.410%
4	147	60	161	++		0.360%
5	157	60	85	+		
6	157	60	96			0.380%
7	157	70	88			
8	157	80	85			
9	157	100	42			0.380%
10	157	100	41			
11	160	100	31			0.270%
12	148	80	41			
13	148	80	38			0.220%

TABLE II

DIABETIC TABLE IN THE CASE OF HERNANDEZ AND BENAROS.

Dates	Units of Insulin	Glucose, gm.	Sp. Gr. of Urine	Glycosuria in Per Cent	Acetone in Urine	Diacetic Acid in Urine
March 23	80	100	1 030	8.5%	+++	+++
March 25	100	100	1 026	4 6%	+	+
March 28	70		1 016	3 0%	0	0
April 7	20		1 023	0 33%	0	0

Later glycosuria disappeared altogether. Then the patient committed some dietary indiscretions following which he relapsed into a state of pre-coma with the following findings:

April 18	80	100	1.030	7.0%	+++	+++
April 20	80	80	1 030	7 0%	+	0
April 22	60		1 030	1 25%	0	0
May 3	60		1 023	4.4%	0	0
May 6	60		1 022	1.43%	0	0

to bring the blood sugar down to the normal level because extreme reductions in the sugar content of the blood took place as soon as the normal level was approached by increasing the insulin dosage or decreasing the total available glucose value of the diet, and sometimes without any apparent reason. For instance, at one time the patient, after being for three days on a diet of 145 gm. and for two days on one of 140.6 gm. and of 160.6 gm. of available carbohydrate and 48 units of insulin (given in 3 doses, 20, 10, 18), had a fasting blood sugar of 0.272 per cent. The following day the insulin was increased to 63 units (given in four doses, 16, 16, 11 and 20), but that afternoon after only 32 units were given instead of the usual 30, the patient had a very severe insulin reaction during which his blood sugar was found to be only 0.016 per cent. Corresponding to the sharp falls in the blood sugar level, we also have sudden elevations of the same. For example, at one time the patient, after being on a diet of 128.5 gm. of available carbohydrate with 45 units of insulin for four days, had a very severe insulin reaction after his carbohydrate intake was decreased by 20 gm. for one day. During this reaction 710 cc. of orange juice containing 71 gm. of glucose had to be given, and the next morning the blood sugar was found to be 0.317 per cent. It is also of interest to note here that only four days prior to this insulin reaction the patient's blood sugar was 0.275 and that only on the preceding day his urine gave a moderately positive test for sugar. Moreover, the next day after the blood sugar was 0.317 per cent, the patient again had a very severe insulin reaction, during which his blood sugar was found to be 0.039 per cent. After this insulin reaction was controlled by administration of 450 cc. of orange juice containing 45 gm. of glucose, the patient went for four days without reactions. It must be emphasized that all these performances were going on with very small or without any changes in the insulin dosage or diet, and that the co-operation of the patient was above reproach. During the two months which the patient spent in the hospital, many attempts were made to bring down his blood sugar level, but insulin reactions invariably took place. He had a total of seventeen insulin reactions while in the hospital. From some seventeen blood sugar determinations we were able to establish the fact

TABLE III (1)
Hospital diabetic table in our Case No. 3.

Date 24 Hours Ending A. M. of	DIET				In- sul- lin Units	Wgt., kgm.	Fluid Intake	URINE				BLOOD		REMARKS
	P	F	CH	Calo- ries				Vol.	Sug.	Acet.	Lia- cetic Acid	Sugar %	Plasma CO ₂ Vol. %	
11/21/26 1:30 P.M.			20	80	25	50.8	200		H*	M**	O	0.336		Patient admitted to hospital in dia- betic acidosis. Weighed in paj- amas and night gown.
3:30 P.M.			20	80	25		400		H	M	O			
5:30 P.M.			20	80	25		200		M	O	O			
7:30 P.M.			40	160	25		1000		O	O	O			Severe insulin reaction.
9:30 P.M.			100	400	75		2650		O	O	O			
5:30 A.M.			200	800	175		4450	3400						
25	20	13½	180	920	40		3600	3580	S***	O				Severe insulin reaction at 10 A.M. Sugar found in the lact of 8 specimens.
26	43½	63½	90¾	1130	30		2050	1950	s m m o	O		0.150		
27	50	85	90	1325	20		3525	2550	o f o o	O		0.106		
28	50	85	90	1325	30	48.3	1950	1750	o m m	O				Cramps in the legs have disappeared.
29	50	85	70	1245	20		2650	2600	o s s	O		0.208		
30	50	85	70	1245	20		2650	2600	o s s	O		0.208		

* Heavy trace. ** Moderate trace. *** Slight trace (capital letters indicate that all specimens of the day gave same result).

TABLE III (2)

Date 24 Hours Ending A. M. of	DIET				In- sulin Units	Wet., kgm.	Fluid Intake	URINE				BLOOD		REMARKS
	P	F	CH	Calo- ries				Vol.	Sug.	Acet.	Dia- cetic Acid	Sugar %	Plasma CO ₂ Vol. %	
30	50	85	90	1325	20		3750	3500	s s m m	O		0.218		Rose Bengal liver function test-- normal.
12/1	50	85	110	1405	55		3000	3200	H	O		0.132		B. M. R. plus 19.6
2	50	85	70	1245	45		1900	1500	m h o	O				B. M. R. plus 34.4
3	50	85	90	1325	45		2500	2350	c h m	O				
4	50	85	90	1325	45		2000	1500	s m c	O		0.275		
5	50	85	90	1325	45	48.1	2500	2100	c m o	O				
6	50	85	90	1325	45		3000	2750	O					
7	50	85	70	1245	45		2800	1700	c m o	O				B. M. R. plus 19.5
8	50	85	161	1609	45		2500	2300	O					Very severe insulin reaction lasting from 7 P.M. to 10 P.M. Icteric index 11.
9	50	85	70	1245	45		3500	3300	s h o	O		0.317		

TABLE III (3)

Date 24 Hours Ending A. M. of	DIET				In- sulin Units	Wgt., kgm.	Fluid Intake	URINE				BLOOD		REMARKS
	P	F	CH	Calo- ries				Vol.	Sug.	Acet.	Dia- cetic Acid	Sugar %	Plasma CO ₂ Vol. %	
10	50	85	115	1435	45		2800	2100	O			0.039		Very severe insulin reaction from 9 P.M. to 10 P.M. Blood sugar taken during the reaction.
11	50	85	70	1245	45		3500	3300	s o o	O				
12	50	85	70	1245	45		2800	2750	O					
13	50	85	70	1245	45		1200	1200	O					
14	50	85	90	1325	45	47	2900	2400	O					
15	50	85	90	1325	45		1730	1350	o s o o	o s o o				Moderate insulin reaction at 8:30 P.M.
16	70	150	90	1090	48		1800	1500	O	s o o o				
17	70	150	90	1900	48				O	s o o o				
18	70	150	90	1090	48	47.4	2700	900	O	S				
19	70	100	90	1540	48		1150	1000	O	S				
20	70	100	110	1620	48		1100	950	O	S				Moderate insulin reaction at 7:30 P.M.
21	70	100	90	1540	48		2100	2000	o s o	o o s		0.272		

TABLE III (4)

Date 24 Hours Ending A. M. of	DIET				In- sulin Units	Wgt., kgm.	Fluid Intake	URINE				BLOOD		REMARKS
	P	F	CH	Calo- ries				Vol.	Sug.	Acet.	Dia- cetic Acid	Sugar %	Plasma CO ₂ Vol. %	
22	70	100	148	1772	63		2400	2000	O.	s o		0.016	69.7	Very severe insulin reaction at 2:30 P.M., 20 cc. of 50% glucose so. given intraven. Blood sugar taken during reaction. Icteric index 8.1.
23	70	125	100	1805	16		1600	1100	O	O				Moderate insulin reaction at 11 A.M.
24	70	125	110	1845	46		2050	1900	o s	O				Moderate insulin reaction at 6:30 P.M.
25	70	125	110	1845	40		1900	1850	o s	s o				Slight insulin reaction at 1:00 P.M.
26	70	125	90	1540	40				O	O				
27	70	125	110	1845	40	47.2	1900	1800	O	O				Moderate insulin reaction at 5 P.M. B. M. R. plus 10.6.
28	70	125	90	1765	40		1600	1550	O	O				
29	70	125	114	1861	40				O	O				
30	70	125	90	1765	40		2100	1500	O	O				Slight insulin reaction at 5:30 P.M.
31	70	125	90	1765	40		1900	1500	O	O		0.256		
1/1/27	70	125	90	1765	60		2200	1800	O	O				
2 to 4	70	125	90	1765	40	47.4	Aver. 2060	Aver. 1317	O	O				
5 to 9	70	125	90	1765	45		Aver. 1920	Aver. 1770	O	O		0.191	65.3	Blood sugar and CO ₂ tension of plasma taken on 1/6/27. Icteric index 10 on 2/7/27.
10	70	125	90	1765	45	47.4	1950	1950	O	O		0.195		

TABLE III (5)

Date 24 Hours Ending A. M. of	DIET				In- sulin Units	Wgt., kgm.	Fluid Intake	URINE				BLOOD		REMARKS
	P	F	CH	Calo- ries				Vol.	Sug.	Acet.	Dia- cetic Acid	Sugar %	Plasma CO ₂ Vol. %	
11	70	125	110	1845	45		1600	1300	O	O				Slight insulin reaction at 2 P.M.
12	70	125	90	1765	45		2450	2150	O	O				
13	46	84	60	1176	30		2350	1700						B. M. R. plus 7.5.
14	46	84	140	1496	45		2300	1700	o o m	O		0.187		Glucose tolerance test done.
15	70	125	107	1833	45				O	O				Moderate insulin reaction at 2:10 P.M.
16	70	125	90	1765	45	47.6	1900	1800	O	O				
17	70	125	123	1907	50		2200	2100	O	O				Severe insulin reaction at 4:25 P.M.
18	70	125	110	1845	50				O	O				Slight insulin reaction at 2 P.M.
19	70	125	114	1861	50				O	O				Slight insulin reaction at 3:30 P.M.
20	70	125	90	1765	49				O	O				
21 to 28	70	125	90	1765	49	47.3			O	O		0.196		Blood sugar and weight taken 1/23/ 27. B. M. R. on 1/26 plus 4.1. Rose Bengal test normal on 1/27/27
29	70	125	190	2165	49	47.3			o o m	O		0.156		Levulose tolerance test done. Patient transferred to Medical Clinic.

TABLE IV
Out-Patient Department diabetic table in our Case No. 3.

Date 24 Hours Ending A. M. of	DIET				In- sulin Units	Wgt., kgm.	Fluid Intake	URINE				BLOOD		REMARKS
	P	F	CH	Calo- ries				Vol.	Sug.	Acet.	Dia- cetic Acid	Sugar %	Plasma CO ₂ Vol. %	
30 to 2/7/27	70	125	90	1765	49	49.3			O			0.103		Patient weighed in clothes for which 10 lbs. is subtracted. Blood sugar taken 2:30 P.M. (after lunch) on 2/7/27. Icteric index 10.
8 to 14	70	125	90	1765	49	50.5			O					Patient weighed on 2/14/27.
15 to 21	70	125	90	1765	49	53			O					Patient permitted to resume work as night watchman. Patient weighed on 2/21/27.
22 to 3/7/27	70	125	90	1765	49	56.2			O					Patient weighed on 3/7/27. Ankle edema.
8 to 15	73	125	106	1841	49	56			S	O	O			Patient weighed on 3/15/27. Digi- talis gr. i, t. i. d.
16 to 22	73	125	106	1841	49	56.4			M	O	O	0.250		Patient confesses to have eaten a small extra sandwich in the P.M. for the last "couple weeks." Icteric index 12.5. Blood sugar and weight at 11 A.M. (before lunch), on 3/22/27.
23 to 29	73	125	106	1841	55	56.2			O					Patient weighed on 3/29/27. Ankle edema gone.
30 to 4/7/27	73	125	106	1841	55	56.2			O			0.119		Two slight insulin reactions in the P.M. relieved by half a lump of sugar. Blood sugar and weight taken 11 A.M. (before lunch) on 4/7/27.
8 to 12	73	125	106	1841	55	57			O					One slight insulin reaction shortly before noon meal. Patient weighed on 4/12/27.

that the patient was reasonably safe from insulin reactions only when his blood sugar was in the neighborhood of 0.2 per cent.

Another remarkable feature of this case is the peculiar character of the insulin reactions. The severity of some of these reactions is the first thing to arrest one's attention. A typical severe reaction would set in with flushing of the face, excessive perspiration and complaints of hunger. A little later the patient would become restless and toss about in his bed in a state of mild delirium, saying things in a rambling way, of which he would have no recollection later. After this the patient would become comatose, his face very red, his eyes staring with the pupils dilated, his skin cold, and his finger tips cyanotic. The length of time and amount of glucose necessary to bring the patient out of these reactions is not less remarkable, for instead of the usual five minutes and 100 cc. of 10 per cent glucose in orange juice given by mouth, which suffice to stop an insulin reaction in an ordinary case of diabetes, it required, in the most severe of his reactions, three hours' time and 710 cc. of 10 per cent glucose in orange juice by mouth before the patient was normal again. There were several occasions when an hour was necessary to bring about recovery from the reaction.

These two characteristics of the more severe reactions of the patient even raised doubts in our minds as to whether they were caused by hypoglycemia. Therefore, blood sugar determinations were made during two of these reactions and the results of 0.039 per cent and 0.016 per cent definitely established the fact that there existed true hypoglycemia. In an attempt to throw some light on the slowness of recovery from these reactions, 20 cc. of a 50 per cent glucose solution was given to the patient intravenously after 200 cc. of orange juice with 24 gm. of glucose by mouth failed for 15 minutes to rouse him from semi-coma, with the result that consciousness returned to the patient in half a minute after the injection was started, and about one minute later the patient was entirely over his reaction.

After ruling out dietary indiscretions and failure on the part of the patient to eat all of his food, the sharp fluctuations in the blood sugar level can be explained in two ways. In the first place, it is feasible that heavy deposits of pigment in the gastro-intestinal tract have brought about a serious impairment

of the absorptive power of its mucosa so that the insulin given before the meal had time to bring about hypoglycemia before the carbohydrate furnished by the meal became available. The extreme prolongation of the time necessary for recovery from an insulin reaction after oral administration of glucose and the prompt response following the giving of it by the intravenous route seemed to support this view. But, on the other hand, insulin reactions have not occurred after every meal, nor after the same meal when they did occur, so that a somewhat intermittent or at least variable functional impairment of the mucosa of the digestive tract must be invoked to explain all facts in the case. To test this theory, a fasting blood sugar determination was made, following which the patient was given 80 gm. of glucose (or 1.7 gm. per kgm. of body weight) by mouth and samples of blood taken every half hour for two hours. The resulting curve was found to possess the same character as similar curves in cases of simple diabetes mellitus (see Chart 1). Likewise, a blood sugar curve obtained after 100 gm. of levulose were given to the patient orally proved to be even higher than similar levulose curves in three cases of simple diabetes recently reported by Root and Baker. These two tests we take to prove a more or less normal absorptive power of the gastrointestinal tract at the time of the tests which were made when the patient was not in an insulin reaction.

Another explanation for the instability of the blood sugar level in our patient is that pigment cirrhosis of the liver has brought about an impairment of the glycogen storing capacity of this organ, thus making the blood sugar level more subject to fluctuations, depending on the two opposing factors, the dosage of insulin and the carbohydrate intake. It is easy to see how an impending insulin reaction which, in a case of simple diabetes, would be warded off by release of the glycogen stored in the liver, would be precipitated in a case where the glycogen stores in the liver are reduced. The same, of course, applies to steep rises in the blood sugar level in the face of an impaired capacity of the liver to take up some of the excess of glucose for storage as glycogen. As a means of investigating the functional status of the liver as regards its participation in the carbohydrate metabolism of the body in the presence of diabetes, the levulose tolerance test was used as the only one available. After

oral administration of 100 gm. of levulose, the blood sugar level showed an increase of 51 per cent at the end of the first hour, and one of 80 per cent at the end of two hours. When compared to the already mentioned levulose curves in three cases of simple diabetes in which the maximum increase of the blood sugar level at any time amounted to only 33 per cent, it will be seen that if any reliance at all can be placed on this test, it is strongly in favor of the second theory. The probability that disturbance of the sugar level regulating function of the liver is a contributing factor in the sharp falls of the blood sugar level in our patient is supported by experiments of Mann and Magath, who found that hypoglycemia was invariably produced in dogs subjected to removal of the liver. On the clinical side Klein and Holzer have observed prolonged hypoglycemia after insulin administrations covered with the theoretical amount of carbohydrate in non-diabetic patients with liver damage from such diverse causes as hepatitis, catarrhal jaundice, carcinoma, cirrhosis, and lues.

The third point of interest that came up in our patient in connection with insulin therapy is the tendency to the formation of acid bodies, which has already been noted by Hernandez and Benaros in their patient. Three weeks after entry the patient, while on a diet of 127.5 gm. available carbohydrate with a fatty acid glucose ratio of 0.76, began to show a trace of acetone in his urine. This kept up, as can be seen from Table 3, for eight days in succession, though at no time during this period did he get a diet with a F.A./G. ratio over 1.17. During these eight days the patient had three insulin reactions, the first of which came on in the evening and a trace of acetone was found in the urine voided at noon on the same day and the following morning. One insulin reaction occurred early in the afternoon after a trace of acetone was found in the morning urine, and another took place at 7:30 P.M. on the day when all three urine specimens showed a trace of acetone. Moreover, out of thirteen urine specimens found to contain acetone, only two showed traces of sugar. The fasting blood sugar taken during this period of acetonuria was 0.272 per cent and the CO_2 tension was equal to 69.7 cc. bound as bicarbonate per 100 cc. of blood serum. All of which goes to show that faulty metabolism of fats was present under conditions where, in a case of simple diabetes, we would

have no reason whatsoever to expect it. Such a faulty utilization of fats in our case probably finds its explanation in the pathological condition of the liver which, according to the latest view, has as one of its main functions the production of some intermediate carbohydrate substance from fats and proteins in the process of their utilization. The acid bodies, according to this theory, are improperly metabolized fragments of fat molecules undergoing transformation into this intermediate carbohydrate substance. In the Argentine case mentioned above, this tendency to acidosis had an opportunity to manifest itself more prominently because the patient was not on a weighed diet.

If theories are to be judged by their deductive applicability, this one has in its favor that on the basis of it the severity of diabetes in hemochromatosis and its rapidly progressive course are made less obscure because, instead of a single disturbance of the carbohydrate metabolism of the body due to lack of insulin, as in diabetes mellitus, the power of the liver to manufacture and store glycogen is also impaired, resulting in a rapid piling up of glucose in the blood stream. The deleterious effects of a high blood sugar level on the islands of Langerhans is well known, and since the introduction of insulin has been substantiated by instances of a partial recovery of the pancreas, especially in young subjects, following the removal of the excessive load from this organ.

In addition, the faulty metabolism of fats with its production of acid bodies is another factor aggravating the diabetes. The same theory could also explain the frequently observed spontaneous cessation of glycosuria in terminal stages of hemochromatosis. On the other hand, it must be admitted that we still possess no explanation regarding the slowness of recovery from severe insulin reactions in our patient when glucose was given orally, unless it be assumed that the absorptive power of the gastro-intestinal mucosa is impaired only during and by severe insulin reactions. The two non-fasting blood sugar determinations made in the Out-Patient Department when the patient was adhering to his diet in a strict manner were lower than any fasting blood sugar determinations, excepting one, made during the patient's stay in the hospital. This fact, in conjunction with the absence of insulin reactions, suggests that the prolonged insulin therapy may have been instrumental in bringing about an

improvement in the carbohydrate regulating mechanism of the body by increasing the glycogen storing capacity of the liver.

On the whole, then, our experience with insulin therapy in this case shows that the patient with hemochromatosis can be rescued from diabetic acidosis and carried on a maintenance diet with reasonable safety provided the blood sugar level, at least at the beginning, is permitted to stay up in the neighborhood of 0.2 per cent. The liver damage resulting in impaired glycogenesis and faulty metabolism of fats finding their expression in the ease with which severe insulin reactions take place and a tendency to acidosis makes the prognosis of the diabetic part of hemochromatosis less favorable than that of simple diabetes. The high blood sugar level per se appears to be rather innocuous, as Maclead's experiments with depancreatized dogs tend to demonstrate. These depancreatized dogs had high blood sugar levels for as long as three years without any impairment of general health (personal communication).

COURSE IN THE HOSPITAL AND OUTCOME

Little needs to be said about the two earlier cases. The first patient was in the hospital for eleven days and, during this brief space of time, progressive deepening of the pigmentation of the skin and rapid enlargement of the left lobe of the liver, probably due to carcinoma, were observed. Also, a steady loss of weight was noted. Ten days after entry the patient had a profuse gastric hemorrhage and died on the following day. His fatal hemorrhage we can assume to have taken place from oesophageal varices, though the exact source of it was not proven at autopsy. Thus, the fatal outcome of this case was due to a complication of the primary carcinoma of the liver.

Our second case was in the hospital but one day and succumbed to diabetic coma, which, in the pre-insulin days, was the usual lethal factor in hemochromatosis. Cirrhosis of the liver in this case was entirely latent.

Our third case was saved from diabetic acidosis with insulin and glucose and treated at the hospital for two months. After that, the patient was transferred to the Out-Patient Department where, at the present writing, he has been under observation for three and one-half months. The therapeutic agents used

were rest, diet, and insulin administration. Ephedrin for hypotension was given to the patient for a while, but later discontinued because of the tendency of this drug to produce hyperglycemia, analogous to that taking place after epinephrine administration. While under treatment at the Out-Patient Department, the patient was put on *Digitalis folia* gr. i. for mild congestive failure of the heart, as shown by the appearance of ankle edema.

At the end of his hospital stay, the patient was markedly improved, and after a month's treatment at the Out-Patient Department he was able to resume his work and continue with it to date without any bad results.

At the end of the first month the patient's diabetes was controlled and the blood sugar level stabilized, as pointed out before, at about 0.200 per cent on a diet of P-70, F-125, and Ch.-90, with a total available glucose value of 143 gm., a F.A./G. ratio of 1, and containing 1765 calories (or 37 C. per kgm. of body weight). A total of 49 units of insulin a day were required in three doses of 20, 17 and 12 units. During this month the patient had three very severe, two severe, four moderate and one slight insulin reactions.

During the patient's second month in the hospital, his urine was sugar and acetone free, and he had only one severe, two moderately severe and four slight insulin reactions while final adjustments of the insulin dosage were being made. During the first month after discharge from the hospital, the patient had no insulin reactions and his urine remained sugar free. (See Table IV) The blood sugar 10 days after discharge was 0.103 per cent. After the patient went to work, he felt so hungry that he added a small sandwich to his diet in the afternoon without a corresponding increase in the insulin dosage. Consequently, at the end of a week, his urine showed a slight trace of sugar and at the end of two weeks a moderate trace of sugar with a blood sugar of 0.250 per cent, but no acetone or diacetic acid in the urine. The patient was allowed to have this additional sandwich in the afternoon and six units of insulin were added to his daily dose, giving him a diet of P-73, F-125, Ch.-106, with a total available glucose value of 161 gm., a F.A./G. ratio of 0.9 and contained 1841 calories (or 32.3 C. per kgm. of body weight), with a total of 55

units of insulin given in three doses of 20, 20 and 15 units. Following this the urine became sugar free and the blood sugar went down to 0.119 per cent, but the patient had three slight insulin reactions controlled by the taking of half a lump of sugar. The severe cramps in his legs, which probably can be ascribed to a diabetic neuritis, went away four days after entry. During the first three weeks of hospitalization, the patient continued to decline in weight and went from 49.8 kgm. to 47 kgm., but during the fourth week gained one-half a kgm. and then remained stationary for a month until the time of his transfer

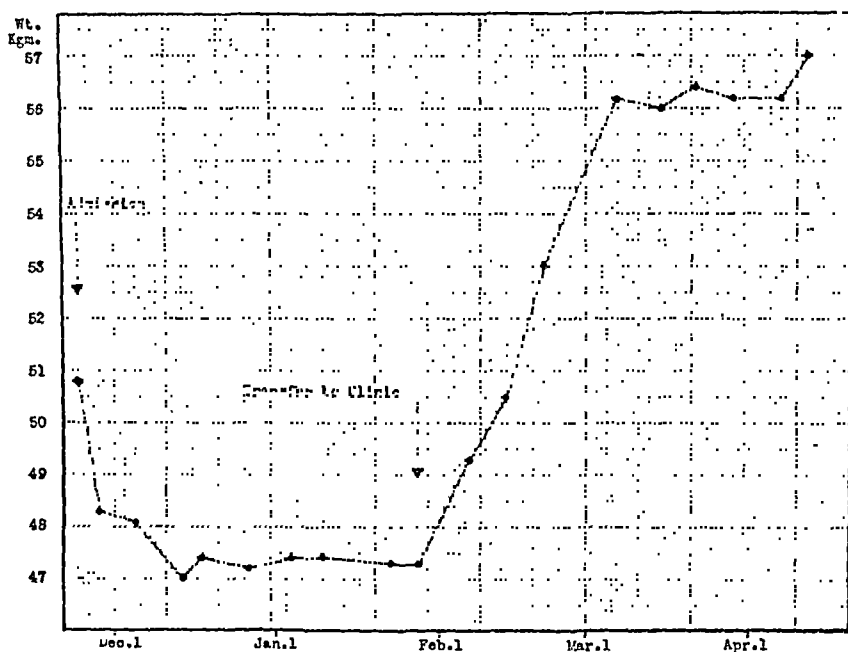


Chart II. Weight curve in Case No. 3 while under treatment in the hospital and at the Out-Patient Department.

to the Out-Patient Department. While under observation there, he gained 9.5 kgm. in two and one-half months (see Chart 2). The basal metabolic rate gradually came down from a peak of 34.4 per cent plus to 4.1 per cent plus (see Chart 3). The icteric index came down, while the patient was in the hospital, from 11 to 8.1, and again went up to 10, and later to 12.5 after the patient's discharge.

The pigmentation of the patient's skin and, therefore, pre-

sumably also deposits of pigment in the internal organs, after a temporary increase during his stay in the hospital, definitely decreased while under observation at the Out-Patient Department.

The conclusion drawn from this is that insulin therapy is able to control the diabetes of hemochromatosis with its direct and indirect manifestations and, in addition, seems to have some beneficial influence on the fundamental pathological processes responsible for hemochromatosis.

SUMMARY

1. Three cases of hemochromatosis are reported: One of

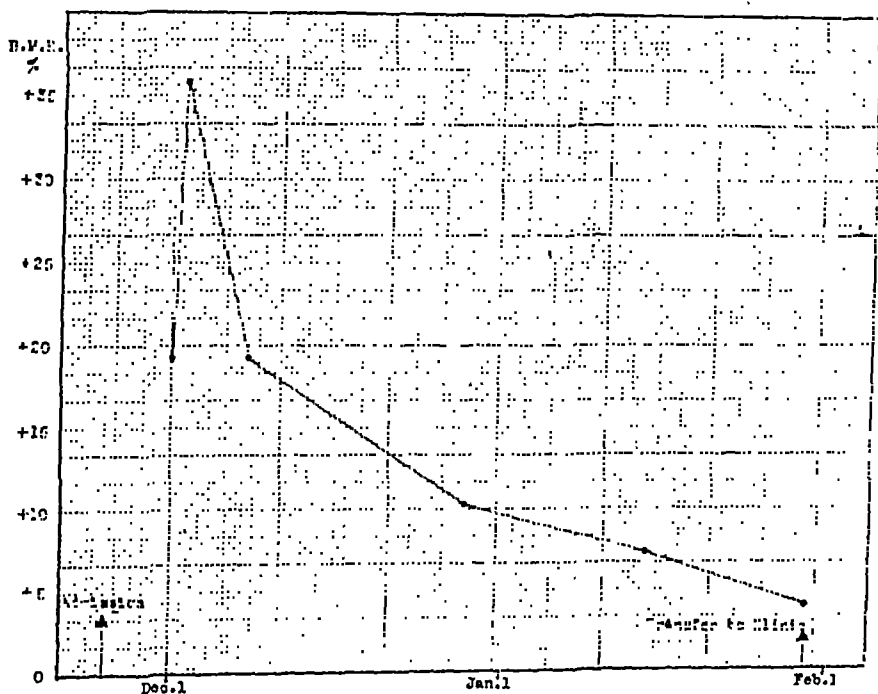


Chart III. Basal metabolic rate in Case No. 3 during the patient's stay in the hospital.

simple hemochromatosis without diabetes, one of hemochromatosis without skin pigmentation, and one classical case.

2. The three main features of the disease, pigmentation of the skin, diabetes, and cirrhosis of the liver, are discussed, as well as two complications of hemochromatosis—primary carcinoma of the liver and sexual regression.

3. The results of insulin therapy are reported, showing

that the diabetes of hemochromatosis differs from simple diabetes mellitus in three respects: Marked instability of the blood sugar level, unusual character of insulin reactions, and tendency to acidosis.

4. Two explanations are offered to account for these differences: Impairment of the power on the part of the liver to regulate carbohydrate metabolism, and diminished absorptive capacity of the gastro-intestinal mucosa.

CONCLUSION

Insulin therapy in hemochromatosis serves to prolong the patient's life by controlling the diabetes, and seems to have some beneficial influence on the underlying disturbance of iron metabolism.

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state of the nervous system. Urinary symptoms, however, are not wanting in many instances of hypothyrosis, though they are usually of a minor nature. We may encounter simple polyuria, strangury, and tenesmus, or a combination or alternation of two or all these disorders.

The studies in this report are based on the analysis of one hundred consecutive cases of hypothyroidism with reference to the urinary function and the pathological changes found in the urine, in addition to a brief report of an hereditofamilial group of endocrinopathic individuals with predominating hypothyroid symptoms.

This family resides in southern Maryland and Virginia and consists of father, mother and eight children. During the past fourteen years the mother and seven of the children consulted me. A brief report of these cases abstracted from my records follows:

Case 1. Mrs. Q. at the time of her first examination in April, 1915, was forty-eight years of age. She was five feet in height and weighed 187½ pounds. She gave a history of delayed puberty until the age of eighteen and a half years; obesity with hypothyroidism pre-existing for a period of ten years. Her chief symptoms were drowsiness, mental dullness, physical sluggishness, inability to concentrate, impairment of memory, muscular weakness, palpitation, dyspnoea, constipation, amenorrhoea and frequent burning micturition. The urine contained a few hyaline casts and an enormous quantity of squamous epithelium (three plus). She voided 1800 cc. in twenty-four hours and the "phthalein" elimination was 67 per cent in two hours. After the administration of thyroid for one month her hypothyroid symptoms subsided, bladder function became normal and the urine free from casts. In December, 1915, seven months later, she reported that her health remained good while taking thyroid; menstruation had returned and the bladder symptoms were controlled. However, after discontinuing thyroid she had a return of her hypothyroid symptoms, including amenorrhoea and vesical irritability; the latter at times was very annoying. In June, 1917, the urine contained pus cells, hyaline casts and an excessive amount of bladder epithelium. An examination of the urine in April, 1918, showed an absence of pus cells but a considerable amount of albumin, a few hyaline casts and many epithelial cells.

In June, 1919, she again complained of vesical irritability with burning and increased frequency of micturition, causing her to void every hour or two during the day and two or three times during the night. She was not seen again until October, 1926, when she stated that her chief complaint was frequent and painful urination, asso-

ciated now with pain in the right side of the abdomen and posterior lumbar region. She had not taken any thyroid for six years with the result that she again exhibited all the characteristic symptoms of myxoedema. There was marked tenderness of the ureteral points on the right side, especially the one located several centimeters outside the umbilicus, recently described by Legge. The urine was entirely negative at this examination. Cystoscopic examination by Dr. Goldstein revealed a reddened mucosa in the region of the trigone and some injection of the bladder mucosa. Further urologic studies revealed a right ureteral kink with hydronephrosis and nephrop-tosis.

Case 2. Mrs. C. was examined in October, 1914. She was 35 years old, five feet three and a half inches tall and weighed 155½ pounds. Her complaint was that for years she suffered with pollak-yuria and backache. The menstrual history was negative. She had patchy pigmentation on the face and forehead. She consulted me again in September, 1926, twelve years later. At this time she gave a history of nocturia, lumbar pains referred to the right groin and irritation at the urethral orifice, for which she had received local treatments. She had reached her maximum weight of 176 pounds three months previous but her weight was then 168 pounds. She exhibited a definite clinical picture of hypothyroidism. The symptoms included lassitude, impairment of memory, intolerance to cold, tinnitus aurium, muscae volitantes, dry, thick, infiltrated skin, falling hair, crunching joints, prominent acra, dulled expression, bradycardia (60), hypotension (92/60) and hypothermia (97.6). She had pyor-rhoea and periapical abscesses. There was pain on pressure over the right posterior lumbar area and the ureteral points were tender. The urine contained many squamous epithelial cells but was other-wise negative. The urplogic examination showed some redness of the external meatus and the trigone was congested and oedematous. Ureteral catheterization and uretero-pyelograms showed hydronephro-sis of the right kidney with a probable stricture of the upper major calyx and ureter on the right side. The condition improved on thy-roid, diet and ureteral dilatation.

Case 3. Mrs. M was examined in July, 1926. She was forty-two years of age and five feet, two and a half inches in height; her maxi-mum weight (in 1918) had been 185 pounds. At the time of examina-tion she weighed 128 pounds. There was fat dystrophy of the hypo-physeal type with marked girdle adiposity. The hypothyroid symp-toms were milder than those in her two sisters just described. As a child she suffered from malaria and at the age of fourteen from rheu-matic fever which was followed by chorea. She gave a normal men-strual history; she had had two normal pregnancies. Her chief com-plaints were chills, fevers and sweats and her diagnosis was malaria. She also complained of pain in her back, aching thighs and nocturia. Foci of infections were found in her tonsils and teeth. The blood was

negative for malarial parasites but showed a moderate grade of secondary anemia with a hemaglobin of 68 per cent, red cell count of 3,318,000 and a leucocytosis of 17,200 with 91 per cent of polymorphonuclear cells. The urine contained albumin and clumps of pus cells. Urologic studies revealed pyelitis of the right kidney which was promptly relieved by treatment.

Case 4. Mrs. H. B. was first seen in July, 1915. She was forty-five years of age, measured five feet and one-quarter inches in height and weighed 175½ pounds. The obesity was of the hypophyseal type with enormous hips and buttocks but most of her symptoms were referable to thyroid deficiency. Her most distressing disorder was asthma from which she suffered periodically. She did not complain of any bladder symptoms and the urine was negative except for epithelium which appeared in large quantities. Her general health improved on the administration of thyroid and anterior pituitary lobe; her weight decreased 26½ pounds, the fat was redistributed and the asthmatic attacks diminished. The epithelial cells in the urine decreased from three plus to one plus.

Case 5. E. E. B. consulted me in April, 1917, at the age of forty-two, for symptoms of myxoedema, obesity and hypertension. The symptoms of myxoedema were so pronounced that he was both mentally and physically incapacitated for many months. He was approximately five feet eight inches in height and weighed 223 pounds. His blood pressure was 205, systolic, and 120, diastolic. One of his chief symptoms was frequency of urination with nocturia. The records of the urinary analysis showed a remarkable fluctuation in character. An examination in April, 1920, was negative except for a trace of albumin. Three months later it contained a large amount of albumin, hyaline and granular casts, fifty pus cells to the field and a large amount of bladder epithelium.

In 1924 red blood cells appeared in the urine with a trace of albumin and a large amount of sugar. In 1925 red blood cells were again found, albumin was present as a trace but there were no casts and sugar was absent. The "phthalein" output ranged from 30 to 47.5 per cent in two hours. The prostate was slightly enlarged. No complete urologic examination was made. By periodic administration of thyroid a good state of health was maintained, including normal bladder function, and by diet the accompanying obesity and diabetes was controlled and the blood pressure was reduced almost to normal. In 1920 he was regarded as a case of chronic nephritis but since then albumin practically disappeared from the urine, casts entirely disappeared and the functional capacity of the kidneys increased.

Case 6. R. B. presented himself for examination May, 1918. He was forty-one years of age and complained of languor, somnolence, amnesia and other symptoms of hypothyroidism and gave a history of gaining in weight. He also complained of having to void frequently during the day and night and of a burning sensation at times. He

passed a normal stream. The only specimen of urine examined was normal.

Case 7. H. T. B. was examined in 1915. He was fifty-one years old and weighed 166 pounds, although his maximum weight had been 225 pounds four years previous. He gave a history of intermittent hematuria with frequent and often painful micturition. He had symptoms of thyroid deficiency. The urine contained 4.3 per cent of sugar and frequently a large amount of blood and pus. A urological examination showed a malignant papilloma of the bladder from which he subsequently died.

Case 8. Mrs. H. B., the mother, was examined in June, 1915. She was sixty-eight years old and complained of pain in the right side of the abdomen. She was short in stature, weighed 160 pounds and was described as obese with puffiness of eyelids and pendulous abdomen due to fat. The records do not contain any references to the urinary function or examination of urine. She died at the age of 72 from pneumonia. No history was obtained of the father except that he was of medium height, obese, weight about 230 pounds, suffered from asthma and died at the age of seventy-two from paralysis.

One son, who was not examined, was five feet, six and a half inches in height, weighed about two hundred pounds, also suffered from bronchial asthma and died from pneumonia at the age of 52.

One of the outstanding features in this group of cases is the hereditary tendency to endocrine disturbances with obesity. While the thyroid function was apparently disturbed in the entire series, in certain cases other glands were affected, namely, the pituitary, as indicated by the type of obesity in two of the daughters; the gonads, as indicated by amenorrhoea and sterility in one; and the pancreas as indicated by glycosuria in two of the sons. Besides, three suffered with asthma. Other striking features are the clinico-pathologic conditions encountered in the urologic tract. It is also remarkable to note the age period when the symptoms first made their appearance. Six of the seven children consulted me for the first time between the ages of 41 and 51 years and one at the age of 25 years. This suggests that the urologic disturbances are late manifestations in the hereditary form of glandular insufficiency.

The constant association of urologic signs and symptoms in this family group of cases is probably more than coincidence and leads one to suspect an etiological relationship between these disturbances and endocrine imbalance, especially thyroid deficiency. Hertoge recognized this feature in hypothyroidism,

stating that the endothelial cells share in the general feebleness. They are shed prematurely and such cavities as the gall bladder and also the urinary bladder are unprotected from the irritating action of their contents. The bladder being constantly denuded of its epithelial lining is more than usually sensitive to the irritating action of the urine and this alone is responsible for many cases of nocturnal enuresis in children. An examination of the urine in these cases shows the presence of a large number of squamous epithelial cells from the bladder. Hertoge further states that the parents, especially the mother, often exhibit a more or less advanced degree of thyroid defect. Undoubtedly the epithelial lining of the entire genito-urinary tract undergoes nutritional changes with tumefaction causing impairment of renal function and lowering the resistance to trauma or infection. No report on systematic observations of functional elimination in myxoedema has been found. Albumin and casts frequently appear in the urine but true nephritis rarely occurs.

In 100 consecutive cases of hypothyroidism studied by the writer, sixteen were males and eighty-four females. The subjective symptoms noted in order of frequency were nocturia, pollakiuria, dysuria, oliguria and incontinence. Forty-three patients complained of nocturia. Of these, twenty-one voided on an average once during the night and twenty-two voided at least twice, but ranged up to nine or ten times during the night. Twenty-five complained of frequency of urination and seven of infrequency of urination. Twenty-six suffered with dysuria; of these, eleven described the sensation as burning; eight as painful and seven as a sense of discomfort or irritability. Two of the patients suffered with incontinence. The analysis of the urine showed a wide variation in the pathological findings. Bladder epithelium in excess of normal was by far the most constant feature, occurring in sixty-nine of the patients. These were designated as one, two, three and four plus, according to their relative amount. Twenty-six showed one plus; twenty-four, two plus; fifteen, three plus and four, four plus.

Pyuria ranked second, occurring in twenty-eight patients; seven showed it in mild form with ten cells or less to the high field. In eighteen, the specimens contained from ten to fifty

cells to the field and in three, fifty or more cells to the field. Albumin occurred in eight with a decided reaction in six and a trace in two. Casts, usually hyaline, occurred in seven. Red blood cells in various amounts appeared in eight. Sugar was present in nine patients. In two of these only small traces were found.

Renal function was tested in only seven of these cases. The sulphophenolphthalein output varied from twenty to sixty-five per cent. This tabulation does not embrace the disturbances of the genital organs but such symptoms as frigidity, impotence, amenorrhoea and sterility were not uncommon. Among the pathological diagnoses of the urologic tract made in this series of cases may be mentioned pyelitis, cystitis, trigonitis, ureteral strictures, urethral caruncles and papilloma of the bladder.

An analysis of the hundred consecutive cases studied (which does not include the hereditary family group) suggests that there is a definite increase in the incidence of urologic diseases which develops as a sequence of thyroid deficiency and that a careful investigation should be made in regard to the genito-urinary function and that the urine should be carefully studied for pathological elements. The facts elicited should lead one to stress their significance and make an effort to diagnose the milder forms of hypothyroidism early and administer thyroid in order to prevent these complications. One should not lose sight of the fact that heredito-familial myxoedema may possibly be prevented by the administration of thyroid to the expectant mother during the period of gestation.

HEADACHE IN RELATIONSHIP TO OVARIAN DYSFUNCTION*

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LOS ANGELES

Various physical and psychical disturbances have been observed during the menstrual cycle of many women. The most common of these manifestations are physical depression and debility; mental depression verging on melancholia at times; degrees of nervousness, varying from mild restlessness, sleeplessness and irritability, to violent hysteria and collapse; dysmenorrhoea, amenorrhoea and metrorrhagia. Headache, although less frequent than the symptoms mentioned above, is quite often observed during the period of the mensis. Since these symptoms have frequently been observed to disappear with the advent of the climacterium, it is generally believed that they are due to some dysfunction of the gonads. As there are no laboratory methods available accurately to measure or register the relative functions of internal secretions of the human sex glands, all conclusions regarding them must be based upon careful clinical observations.

A review of the histories of 8500 consecutive medical patients in private practice, revealed 47 women suffering from severe headaches during the menstrual cycle. Many of these patients had constitutional factors, which obscured the direct relationship between the headache and the pelvic organs. However, 15 patients with an uncomplicated picture of menstrual headaches, who have been relieved by methods directed toward the correction of the ovarian dysfunction, have been selected for this communication. The factor of psychotherapy has been eliminated. The patients were not advised as to the medication prescribed nor as to the relief to be expected, consequently the disappearance of the headache was a spontaneous response from the patient herself.

This series of cases will be recorded in detail with the

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thought that greater interest may be created in this broad field of clinical observation.

CASE HISTORIES

Case No. I. A married woman, aged 45, complained of headache. The patient stated that she had had headaches more or less all of her menstrual life. They always came at menstruation time, sometimes before and sometimes after the flow started. The pain was mostly in the left temporal region and lasted twenty-four to forty-eight hours. She had continuous headache in the back part of the head for one year. This type of headache appeared after an attack of influenza. Menstruation occurred at regular intervals; the flow was normal in amount and there was no dysmenorrhoea.

General physical examination showed a well nourished woman. The tonsils were moderately enlarged and pus could be expressed from the crypts. The sinuses were cloudy. The blood pressure was 70 diastolic and 98 systolic. The pelvic organs were normal to palpation. The Wassermann test was negative. A complete gastrointestinal study, consisting of fractional test breakfast, stool and x-ray examinations, revealed no abnormality.

The sinusitis disappeared under treatment and with it the occipital headache. The menstrual headache remained unchanged. The patient was given five grains of ovarian substance (Parke-Davis & Co.), three times a day after meals, with no relief. The dose was increased to ten grains, three times a day. After two months' feeding, the menstrual headache disappeared. Two months later the dose was decreased to five grains and for one year there has been no recurrence of the menstrual headache.

Case No. II. A married woman, aged 47, complained of premenstrual headache. She had had headaches at the time of the menstrual period for twelve years. They began after the birth of her child. These headaches were prostrating, incapacitating and lasted from twenty to thirty-six hours. The headache always occurred at the onset of the menses and for the first forty-eight hours the menstrual flow was very scant. The duration of the entire period was four or five days and the flow insufficient. She had always noticed tiredness and nervousness for one week previous to onset of menstruation.

The general physical examination revealed a well nourished woman. The sinuses transilluminated well. The tonsils were enlarged and pus could be readily expressed. The heart and lungs were normal. The blood pressure was diastolic, 70; systolic, 110. There were no unusual gastro-intestinal findings. The fundus of the uterus was in retroposition and the cervix was chronically inflamed. Blood and urine findings were normal.

Ten grains of ovarian substance (P. D. & Co.) was given after meals. After two months' feeding, the premenstrual disturbance

and the headaches disappeared. The flow became normal. The ovarian substance was decreased after four months. There has been no return of the headaches, although one year has elapsed.

Case No. III. A married woman, aged 44, suffered with terrible nervousness, depression and headache around menstruation time. It was a sort of restlessness, associated with marked irritability, headache and melancholia. There was no nausea or vomiting accompanying the headache. For one interval of six months the headache occurred on the right side and would last three days. At other times the pain was general over the entire head. The pain was a dull type of ache and lasted from a few hours to a week, before the menstrual flow started. The menstruation lasted three days, was normal in amount and not associated with any cramping.

Physical examination showed a short, fat woman with no evidence of infection in the sinuses or teeth. The tonsils had been removed. The cardio-respiratory system showed no abnormality. The blood pressure was diastolic, 70; systolic, 130. There was a true achylia gastrica present. Stool, urine and x-ray studies of the gastro-intestinal tract gave normal findings. The pelvic organs were not remarkable.

This patient was given ten grains of ovarian substance (P. D. & Co.) after meals. The headache and the pre-menstrual nervousness were absent at the second mensis after treatment was started. The medication was continued several months and then stopped. During the past four years she has had an occasional return of symptoms, which were relieved promptly by resuming the former medication. The mensis has continued to be regular.

Case No. IV. A married woman, aged 36, had observed severe headaches at menstruation time for many years. The menstruation had been scanty and came at irregular intervals. For several months she had awakened daily with a dull headache in addition to the very acute headaches during the time of the menstrual period. She was exceedingly nervous and felt weak and depressed at all times. There had been two children, but the headaches did not start until after the last childbirth.

Physical examination showed a fairly well nourished, restless and anxious appearing woman with no evident physical defects. The blood pressure was diastolic, 70; systolic 120 and the pulse was 70. The blood, urine, stool, basal metabolism and gastro-intestinal findings were normal.

Because of the irregular and scanty menstruation and the severe morning and monthly headaches, 15-grain doses of ovarian substance (Parke-Davis & Co. preparation) were given three times a day. In addition a 32-grain ampule of Lilly ovarian extract was given hypodermically, three times a week. Within a week after the treatment was started the morning headaches disappeared. After the second mensis the monthly headache was absent. The

menstruation became regular and the flow normal in amount. The doses were gradually decreased. Several months after the treatments were stopped, the above condition recurred and was again relieved by ovarian therapy.

Case No. V. An unmarried woman, aged 26, complained of severe menstrual headaches. The onset of this type of headache was one year ago. The pain started one to two days before menstruation and lasted five to six days after the flow ceased. Occasionally the headaches were associated with nausea and vomiting. For six months the menstrual flow had been scanty and lasted one to two days. She had gained about 20 pounds in weight since the onset of the headaches. Between menstrual periods her health was excellent.

The general examination showed a rather fat woman. The skin, hair and nails were not dry. There was no sinus or oral sepsis. The heart and lungs were normal. The blood pressure was diastolic, 90; systolic, 140; the pulse rate was 72. The gastro-intestinal and generative organs showed no abnormality. The basal metabolism rate was plus six per cent.

The patient was placed on ten grains of ovarian substance (P. D. & Co.) after meals. After the second menses there was no further headache and the menstrual flow became normal in amount and lasted three to four days. She remained free of all headache during the ovarian feeding and for some months after it was stopped. She has been free of this type of headache for six years with only occasional feeding of the ovarian substance for a period of a month or two at a time.

Case No. VI. An unmarried woman, aged 39, had, for several years, marked nervousness at the time of menstruation. The nervousness and menses were always associated with severe headaches. The headaches were incapacitating, general in type and lasted from 24 to 36 hours. Sometimes the nervousness and headache would precede, and at other times, follow the menstrual flow. The menstruation had been slightly irregular and scanty. A tumor of the right ovary had been removed four and a half years previously, but the removal of this tumor did not relieve the headache condition.

General examination revealed a slender woman with cold, clammy hands and feet. The hair, nails and skin were not dry. The sinuses and mouth showed no chronic infection. The blood pressure was diastolic, 70; systolic, 150; pulse 72. The heart, lungs, gastro-intestinal and generative organs were quite normal. The blood Wassermann test and the urine findings were negative. Hemoglobin was 76 per cent; the red blood cells, 4,300,000.

After two months' oral administration of ovarian substances, ten grains, three times a day, after meals, the headache and nervous symptoms disappeared. Recurrences of these symptoms during the past four years have always disappeared after ovarian medication.

Case No. VII. A widow, aged 38, has observed severe headache at the menstrual period for several years. These headaches were associated with nausea and vomiting and lasted from one to two days. She had one or two slight headaches each week, associated with constipation, but the severe attacks always occurred during the menstrual period. She was exceedingly nervous and depressed during the menstrual week. The menstruation was very regular, flow was scanty, but the duration was about five days.

The general physical examination showed a well developed dark woman. The sinuses transilluminated well. X-ray plates of the cranium did not show evidence of intracranial pressure. The tonsils were chronically infected. The heart and lungs were normal. The blood pressure was diastolic, 70; systolic, 120; pulse, 72. The gastro-intestinal and pelvic organs were normal to palpation. A fractional test breakfast showed a hyperacidity. The urine, stools and blood were normal. X-ray studies of the gastro-intestinal tract showed marked colonic stasis.

The constipation was rectified and the intermenstrual cephalalgias disappeared, but the menstrual headache continued. Ten grains of ovarian substance was administered by mouth after meals. After the second month the menstrual headache and nervous symptoms disappeared and the menses become normal. With the aid of intermittent ovarian feeding, she has had no menstrual headache for two and a half years.

Case No. VIII. A married woman, aged 35, complained of headache at the menses. She had given birth to a large baby 19 months previous to examination. She gained weight while nursing the baby and felt splendid. For the past six months she had very severe headaches at the time of the menstrual period. These headaches came on the day previous to the menstruation and lasted for two days. The pain was terrific and located just behind the eyes. She had been very nervous during the menses. Menstruation had been scanty and irregular.

General examination showed an undernourished woman with dry skin, nails and hair. The sinuses were not cloudy. The tonsils and gums were chronically infected. The pulse was 84 and the blood pressure, 80, diastolic; 130, systolic. The remainder of the findings were normal. A blood examination showed hemoglobin, 77 per cent and red blood cells 4,340,000. The basal metabolic rate was plus six per cent.

This patient was placed in a hospital and on forced feeding regained the lost weight, but the headaches at the time of the menses persisted. After two months' feeding of ovarian substance (P. D. & Co.), 15 grains after meals, the monthly headache disappeared and she has remained well for two years.

Case No. IX. A married woman, aged 34, complained of severe nervousness and headaches. She was operated upon four years

previously and abscessed Fallopian tubes and a chronically inflamed appendix removed. The ovaries were not removed. Since the operation she had had very marked nervousness, melancholia, irritability and severe headache at the time of menstruation. The nervous symptoms preceded the menstrual flow several days and the headache two or three days. Occasionally during these attacks of headache she has had deafness in the right ear and some visual disturbances. The menstruation occurred at regular intervals and was practically normal in amount.

General examination showed a poorly nourished, pale, restless woman. The tonsils and gums were chronically infected. The heart, lungs, stomach, intestinal and pelvic examinations were normal. The blood gave a negative Wassermann test. Hemoglobin was 78 per cent and the red blood cells 4,420,000. The urine, stool and fractional test findings were normal. Complete x-ray studies revealed no abnormalities.

The patient was placed in a hospital and, on forced feeding, gained 20 pounds, but continued to have the menstrual headaches and nervousness. She was then given ten grains of ovarian substance by mouth, three times a day after meals. After two months' ovarian feeding, the menstrual symptoms completely disappeared. On intermittent ovarian feeding, she has remained free of headaches and nervous symptoms at menstruation time for four years.

Case No. X. A married woman, aged 43, complained of headache. For several years she had headaches at irregular intervals, always associated with nausea and vomiting. At first the duration of pain was 24 hours, but the time increased to two or three days. These headaches were always worse at menstruation time. At times the headaches started before menstruation and other times at the end of the period. Until 20 years of age, she would have headache about once a month. Between 20 and 30 years of age, there were two headaches a month. For the past ten years, she has had excruciating headaches two or three days every week. She had part of the uterus and one ovary removed three years previously with no relief from the headaches. At times the pain was more acute at the base of the skull, and at other times, above the eyes. The pain was very sharp but not pulsating. She had one child and during the period of pregnancy did not have headaches. The menstruation was scanty, irregular and associated with marked mental and physical depression.

General examination showed a well nourished woman. The skin, hair and nails were in good condition. The sinuses were clear. The tonsils had been well removed. The heart and lungs were normal. The blood pressure was diastolic, 70 and systolic 120. The pulse was 72. Abdominal and pelvic findings were normal. A fractional test meal showed a spurious achylia gastrica. The Wasser-

mann test and blood count were normal. Urine, stool and x-ray study of the gastro-intestinal tract revealed no abnormalities.

The patient was placed on a laxative diet with no apparent change in the headaches. She was then given 15 grain doses of ovarian substance by mouth after meals. After two months' feeding, the headaches disappeared. She has taken ovarian substance at intervals during the past three years and has been entirely free of menstrual headaches.

Case No. XI. A married woman, aged 40, complained of headaches. During her high school days she frequently had headaches. When at college, she began having regular sick headaches at her menstruation time. These were always associated with nausea and vomiting and would last from 24 to 36 hours. The pain was constant in character and general over the entire head. The patient had been married for 15 years and had two children. She had noticed that during each pregnancy she had been free of headache during the entire nine months. Two years ago, she had an abdominal exploratory operation in the hope that some difficulty could be found and corrected, with relief of the headaches. Some adhesions were released, but this gave no relief. The menstruation period had always been regular, every 28 days, rather scanty in amount and lasting only three days.

The general examination revealed no abnormalities. Blood, urine, stool, test breakfast and x-ray studies showed no evidence of organic or functional disorder.

The patient was given ten grains of ovarian substance by mouth after meals and one ampule of Lilly's ovarian extract hypodermically every second day. After the second menses, there were no further headaches. The hypodermic injections of ovarian extract were stopped after two months and the feedings by mouth continued. During the past three years, she has taken ovarian substance by mouth at intervals and has remained free from headache.

Case No. XII. A school girl, aged 17, complained of chronic headache. She had an attack of so-called "intestinal flu" about four years previously. Following this attack, she developed headache. The headache was continuous. She remained in bed for six months following the "flu." A slightly elevated temperature was noted during her pre-menstrual period. During the six months in bed the headache remained constant. She had no other complaints excepting tiredness and lack of appetite. Following the protracted bed rest, she gradually gained strength, but the headache continued. An impacted wisdom tooth and infected tonsils were removed, but this gave no relief from the headaches. The head pain persisted day and night. She became quite nervous and lost considerable weight. The menstruation had started at the age of 11 and was perfectly regular. Since the onset of the headaches, the menses has been scanty and the menstrual nervousness increased.

The general examination showed a pale and poorly nourished child. There was no evidence of sinus infection and x-ray plates showed no head abnormality. There was a slightly impaired percussion note at the right apex, but no rales were heard. The heart valves seemed normal. The blood pressure was 80, diastolic and 98 systolic. The pulse was 72 and the temperature 98.6° F. The abdominal and pelvic examinations were normal. The blood Wassermann was negative and the blood count showed hemoglobin 77 per cent; red blood cells, 4,044,000. The urine and stools were normal.

The patient was given tonics and forced feeding. She gained weight to normal, but the headaches persisted.

Ten grains of corpus luteum, Hynson, Westcott & Dunning, were given by mouth and after two months' feeding, the headaches disappeared. She has remained free of headache for one year although it has been necessary to continue small doses of corpus luteum by mouth.

Case No. XIII. An unmarried woman, aged 25, complained of palpitation of the heart, marked weakness and headache. She had always been underweight and in recent months, weighed 80 pounds. Her height was five feet, six inches. For several months she had marked palpitation of the heart and at times faintness when walking about. She had had almost continuous headaches for many months. The slightest exertion would cause more severe headaches and these would last many days. The headaches were always more acute at menstruation time. For two years the menstruation had been very scanty and irregular. There was marked mental and physical depression at the menstrual time.

Physical examination showed a very tall, very poorly nourished, pale looking girl. The sinuses were clear and the tonsils had been well removed. The lungs were normal. The heart was small and there was no valvular lesion. The blood pressure was diastolic, 70 and systolic, 90. The pulse rate was 80; the temperature, 98.0° F. The abdomen was flabby and the uterus small. The hemoglobin was 70 per cent; red blood cells, 4,000,000. The urine, stool and the Wassermann findings were normal.

The patient was kept in bed for several weeks. She gained weight on forced feeding to 126 pounds. However, the headaches persisted. The bowel movements were regular. The blood pressure was diastolic, 70; systolic, 110, but menstruation continued to be irregular and scanty.

She was given ten grain doses of corpus luteum by mouth and had almost immediate relief from the headaches. The ovarian feeding was continued for three months and then gradually stopped. For three years the patient had remained entirely well.

The thirteen cases presented were those of patients suffering from extremely severe headache associated with the menses.

All possible causes of headache were eliminated before the ovarian feeding was started. The relief occurred within a few weeks. It would appear that ovarian feeding served to restore the function of the ovary so that for varying lengths of time the supply by mouth was not needed.

The following two patients were not relieved of their headache by ovarian therapy, but their cases are recorded as instances of relief of severe menstrual type of headaches relieved by artificial menopause.

Case No. XIV. A married woman, aged 37, complained of headaches that had occurred regularly at the time of menstruation for many years. For one week preceding menstruation she felt terribly depressed, nervous and sleepless. This nervousness was greatly relieved when the menstruation period was passed. The headaches at menstruation time were worse in the back of the head, but at times the entire head ached. The headaches were usually associated with some dizziness and faintness. Nausea and vomiting were always present and lasted four or five days. The headaches usually appeared before the onset of the menstrual flow, but sometimes during and after the period. She became greatly run down, lost much weight, became anemic, chronically constipated and at times had mucus in the stools. Occasionally she would have headaches between periods; these were usually attributed to an intestinal upset. It was of interest to note that she had no headache during pregnancy.

Physical examination showed a frail, undernourished, pale looking woman with a flabby musculature. The tonsils were moderately infected. The sinuses and teeth were normal. The lungs and heart showed no organic disease. Blood pressure was 70, diastolic; 110, systolic; pulse, 72. The abdominal walls were flabby. The pelvic organs were normal to palpation. The blood Wassermann was negative. Hemoglobin was 75 per cent and red blood cells 4,000,000. The basal metabolic rate was plus six per cent. The urine, stool and gastro-intestinal x-ray studies showed no abnormalities.

This patient was kept in a hospital for three months, gained weight to normal and felt better in a general way, but was confined to bed one week out of every four on account of the menstrual disturbances and headache. Menstruation was normal in amount and lasted three to five days.

The patient was given large doses of ovarian substance by mouth as well as hypodermically for five months with no relief of the menstrual symptoms. After one year's observation, the menopause was produced by means of deep x-ray therapy. Since the menstruation was stopped there have been no further headaches. The patient had gained in weight and strength and, aside from slight

discomfort associated with hot flashes, has been in splendid health for one year.

Case No. XV. A married woman, aged 40, complained of headache since the age of sixteen years. Menstruation started at the age of 14. She began having headaches regularly at each menstrual period, the pain lasting from 24 to 48 hours. As she grew older the headaches became more frequent, coming not only at the time of menstruation but also between periods. During the past 25 years there were three intervals of nine months each when she had been free from headaches. The intermissions occurred during each of her three pregnancies. Quite soon after the birth of each child, the menstruation started again and the headaches recurred. For several years she had from one to two headaches every week, so severe that she would be confined to bed for one or two days. At various times during the past 25 years she had had many kinds of treatment for the headaches without relief, she had taken large doses of thyroid, ovarian extract, pituitary extract, etc. The pain in the head usually came on without any apparent cause, starting on one side of the head and later going to the other side and finally both sides of the head ached before the pain ceased. There was no nausea or vomiting at any time. The remainder of her history was unimportant.

Physical examination showed a short, poorly nourished, Jewish woman, with normal skin, hair and nails. The sinuses were free and the tonsils well removed. The teeth were in excellent condition. The lungs were normal. The heart rate was 80; blood pressure 70, diastolic; 120, systolic. The uterus was enlarged to the size of an orange, irregular in shape and hard. The blood showed a negative Wassermann test, a hemoglobin of 80 per cent and red blood cells 4,200,000. The basal metabolic rate was plus 12 per cent. The fractional test meal, urine, stool and x-ray study of the gastrointestinal tract showed no abnormalities. The patient was 25 pounds below normal weight.

By careful feeding she gained in weight from 95 to 118 pounds and the general condition appeared quite good, but the headaches persisted. Because of the fibroid of the uterus, the long history of severe headache and absence of relief from excruciating headache by numerous forms of medication, pan-hysterectomy was advised. This operation was performed, convalescence was uneventful. The patient has been entirely free of headache for four years.

COMMENT

It is noteworthy that the headaches of this small series of cases have shown no uniform characteristics. The localization of the pain has not been constant. In some patients, the pain was general; in others, occipital, temporal or unilateral. The character of the pain has varied from a dull, steady ache to a

sharp, boring pain. The time of the headache in relationship to the onset of the menstrual flow has varied. In some instances the pain was continuous during the entire month; in others, pre or post-menstrual or during the menses; and in some patients, at irregular times during the month.

There were noted rather constant nervous disturbances, which consisted of varying degrees of physical and mental depression, irritability, excitability, sleeplessness and restlessness. In some instances the nervous manifestations were almost psychopathic.

The menstrual cycle itself was upset in various ways. In most cases the flow was scanty and the duration short. Dysmenorrhoea was not a feature. A few patients reported almost normal menstrual flow.

It was interesting to note that four, or all of the subjects who had been pregnant after the onset of their menstrual headache, had observed an absence of headache during the nine months of pregnancy. The headaches returned with the advent of menstruation following the childbirth.

Four patients had been subjected to various surgical procedures in an effort to get relief from the debilitating headaches.

The treatment in this series of cases has varied. All possible causes of the headache were as completely eradicated as possible, including the correction of undernutrition and anemia. Thirteen, or 85.8 per cent of the patients were relieved of their headache by some form of ovarian feeding or medication. In most instances ten to fifteen grains of a reliable ovarian substance were given by mouth. In some cases ovarian extract was given hypodermically in addition. Relief from the nervous symptoms and headaches was obtained within six to eight weeks. The amount of the medication was then gradually decreased during the subsequent two or three months.

One subject had a radical pelvic operation, which gave immediate and permanent relief from the headaches. This patient had a small fibroid uterus, which justified the pan-hysterectomy. The other patient was relieved of her symptoms by the production of the menopause by x-ray. The methods used in these two cases were radical and should not be considered until all other procedures have failed. The physical and mental status

of each of these women was deplorable, but only after prolonged study and observation did such extreme measures seem justifiable.

SUMMARY

A review of the histories of 8500 private patients disclosed 47 suffering from menstrual headaches; of these, 15, whose cases were uncomplicated and who were relieved by treatment of ovarian dysfunction, are reported. It appears that:

1. There is a type of headache associated with ovarian dysfunction.

2. The headache itself is not characteristic, nor does it differ from headaches due to other causes.

3. This type of headache is associated with nervous symptoms and other features of ovarian insufficiency.

4. Relief from these headaches is obtained by correction of the ovarian dysfunction.

5. Two cases are reported of patients who were relieved of their headaches by the production of an artificial menopause.

6. Correct diagnosis is essential if results are to be obtained by ovarian feeding.

A NEW (ORBITAL) METHOD FOR EXTIRPATION OF THE HYPOPHYSIS IN THE PIGEON

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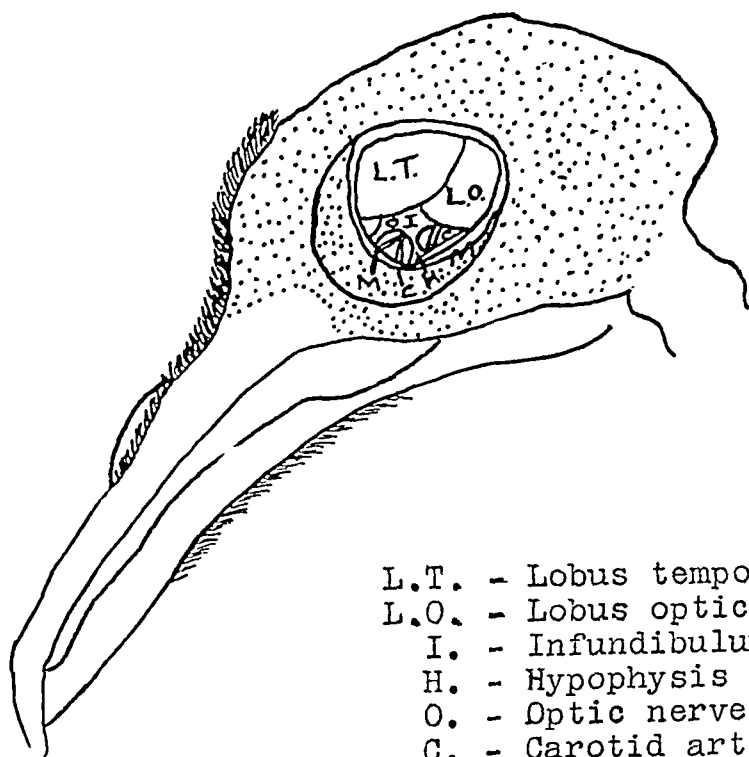
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Pituitary gland extirpation has been performed by many investigators (Biedl, Aschner). In the course of an investigation on the effect of the pituitary gland upon body temperature in the pigeon we were often compelled to ablate the gland. The cranial method (Cushing, Kreidl) was first tried in vain, then the palatine method (Caselli, Gaglio) proved also fruitless. We were thus driven to devise a new method by which the operation was carried out through the orbital cavity.

The eye-ball on one side was enucleated and the intervening bone removed to give access to the mid-brain cavity to permit extirpation of the hypophysis. A skin incision was made about 2 cm. in length along the frontal line just over one eye, and the bone bordering the orbital cavity was exposed. The soft tissues surrounding the eye-ball were first cut away and the latter itself taken out after necessary ligatures. The bony wall of the orbital cavity was removed piece by piece with bone-forceps, beginning at the parietal corner. The exposed cerebral meninges were pressed upwards with a spatula, a small knife was inserted between the bone rest and the meninges, and a small piece of the bone spreading to the chiasma was brought out. Care was taken not to injure a large blood vessel which lies directly under these places, otherwise, in most cases, the animal bled to death. When the cerebral meninges were cut open, the lateral part of the mid-brain and a part of the medulla oblongata were easily seen. Usually the cerebrospinal fluid flowed out, pulsating. Opening the meninges that cover the optic nerve, the latter was cut. A spatula was then inserted from the lateral side of the mid-brain to raise it. The gland could be seen in the sella turcica hanging from the infundibulum, between the oculomotor nerve and the carotid artery (see accompanying figure). In order to widen the site of operation it

was sometimes more convenient to cut the other optic nerve in addition. In most cases, however, this proved unnecessary; the remaining optic nerve was usually untouched and in this manner complete blindness of the animal was avoided. When skill is attained, it is unnecessary to cut even one optic nerve. At last the brain was pressed upwards by the spatula in the left hand and the gland taken out with a sharp curette in the right hand by a single scraping. The operation proceeds more smoothly



- L.T. - Lobus temporalis
- L.O. - Lobus opticus
- I. - Infundibulum
- H. - Hypophysis
- O. - Optic nerve (left)
- C. - Carotid artery
- M. - Oculo-motor nerve
(left and right)

The hypophysis with its surroundings seen through orbital cavity. Left eye is enucleated.

when the carotid arteries are ligated in advance. After the extirpation the lacuna was filled with a piece of cotton. The cerebral meninges need not be sutured. The orbital cavity was also lightly packed with cotton and over it the eye-lids were stitched together. The strict observance of general surgical asepsis is necessary throughout the manipulation.

The body temperature of a pigeon which is deprived of the pituitary gland displays a continuous drop to a certain degree, as is illustrated in the following example:

Date	Temp. of the Air	Time	Body Temperature
19/10		9:00 A.M.	42.1 C.
		12:00	Operation
	21 C.	1:49 P. M.	41.1
	20	2:20	41.0
	19	4:00	40.8
	20	5:00	40.6
20/10	20	6:00	40.8
	20	9:30 A.M.	40.3
	20	10:20	38.7
	20	11:50	39.2
	20	12:00	38.9
	21	1:15 P.M.	39.3
	21	3:30	40.0
	20	4:30	39.9
	21	6:00	39.7
	20	8:40 A.M.	38.9
21/10	20	9:30	38.8
	20	10:00	38.8
	21	11:00	38.9
	20	12:00	39.1
	20	1:15 P.M.	39.0
	20	2:15	39.0
	20	3:15	38.5
	20	4:30	38.5
	20	5:30	38.3
	20	9:20 A.M.	38.5
	20	10:00	36.8
	20	10:30	35.3
22/10	20	11:00	34.9
	20	11:30	34.0
	19	12:00	32.0
		1:00 P.M.	Death

Postmortem examination showed a little blood coagulum in the orbital cavity but no inflammation, infiltration or suppura-

tion of the cerebral meninges or the brain substance. The gland was extirpated completely.

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Book Reviews

THE FLUSHINGS OF THE MENOPAUSE. John H. Hannan, 1927.
Baillière, Tindall & Cox, Lond. Pp. 52.

Hannan has made careful systematic observations over the course of five years upon women at the menopause. He found that the blood-pressure and pulse picture during a crisis is closely similar to that resulting from an intravenous injection of adrenalin. Adrenalin mydriasis could be evoked at this period, hence he postulates sympathetic hyperirritability. The subjective picture of a crisis could be evoked by adrenalin. Thyroid medication consistently aggravated the situation. Ovarian preparations by mouth or hypodermically seemed to improve the condition. Schickele's observation that corpus luteum by mouth is efficacious in reducing hypertension was confirmed. Various other practical topics on the management of the menopause are considered.

DIE ERKRANKUNGEN DER BLUTDRÜSEN. Wilhelm Falta, 1927. J. Springer, Berlin. Pp. 362. (Section in Handbuch der inneren Medizin, Bergman and Staehelin.)

To the readers of this Journal it will no doubt suffice to state that the contents and arrangement of this book of Falta's are quite similar to those of the earlier and well known edition that was translated into English by Meyer. The book is, as its title indicates, clinical in its scope and emphasis, with only such citation of experimental work as bears upon interpretation of symptoms. While no book of this size can treat the topics involved in the subject of endocrine diseases with anything like completeness, the author has in general been judicious in selecting the data included. Perhaps the most outstanding omission is that of recent work bearing on the interpretation of exophthalmic goiter and toxic adenomata—all of which are lumped

together as "hyperthyroidism." The subject of diabetes mellitus is not treated at all.

The book is rather well printed and, though sparingly, is pleasingly illustrated. The publishers, however, went to no short lengths to make the material inaccessible. Topical headings are but sparingly employed and there is neither index nor table of contents in the book itself, these presumably being made up for the Handbook as a whole. The bibliography is particularly trying, being printed as solid running text (58 pages) with no prominence even given to authors' names—among which "Derselbe" occurs with annoying frequency. A bad matter is made worse by a slipshod, inconsistent form of citations, and these not always accurate.

Abstract Department

Medulliadrenal secretion and carbohydrate metabolism. Britton (S. W.) & Gelling (E. M. K.), *Am. J. Physiol. (Balt.)*, 1927, **81**, 467.

Since the introduction of insulin much discussion has arisen regarding the function of the adrenal medulla in its possible relationship to carbohydrate metabolism. Inquiry was made into this problem in the present series of experiments. After having carried out control observations on the response of normal dogs and cats to insulin, medulliadrenal inactivation was performed by the operation of (a), medullectomy and also by that of (b), removal of the right adrenal gland, and denervation of the left. Both types of operated animals, maintained in vigorous health, exhibited striking changes in susceptibility to insulin. Whereas the hypoglycemic reactions were commonly slight or absent on administering two or (sometimes) four units of insulin per kgm. weight before operation, lower blood sugar values and convulsive seizures were often observed following the injection of 0.5 or (sometimes) 0.2 unit per kgm. weight into the same animals after the adrenal medulla had been rendered nonfunctional. The suppression of adrenin secretion in animals therefore resulted in a four to ten-fold increase in sensitivity to insulin. The depression of the sympathetic nervous system by the administration of ergotamine further, but only slightly, accentuated this hypersensitivity. During hypoglycemic prostration in these cases there occurred convulsive fits, interposed by general tonico-clonic contractures, and manifesting a tendency to become confluent in character. The adrenal inactivated animals showed no increase in blood sugar immediately following convulsions. That the glycogen reserves were adequate could be demonstrated, however, by the fact that small amounts of epinephrin rapidly elevated the blood sugar and promoted recovery. Corresponding increments in the glycemia did not occur on giving adrenalin to convulsant animals with adrenals intact. The increased sensitivity to insulin of medulliadrenal inactive animals, has persisted for over three months. Complete protection against the lowering of the blood sugar percentage and insulin shock was nevertheless readily afforded by the administration at suitable intervals, commencing shortly after the administration of insulin, of small doses of adrenalin. Derived from this evidence are the conclusions that a highly potent secretion from the adrenal medulla, tending towards depletion of the

glycogen stores in the body while supplying sugar to the blood stream for use by the important (e.g., nervous and muscular) tissues, takes place during insulin hypoglycemia, and that in the absence of this secretion the glycogen depots although well furnished have a much restricted availability (and that through the medium of the sympathetic nervous system) to the interdependent parts of the organism.—Author's Abst.

Effect of adrenalin on the temperature of skeletal muscle after stopping the venous blood flow through the liver and after stopping both venous and arterial blood flow through the liver. Caskey (M. W.), & Humel (E. J.), *Am. J. Physiol. (Balt.)*, 1927, **81**, 280-283.

In previous studies it was shown that ligating the blood vessels at the hilus of the liver prevented the thermogenic effect of adrenalin in the skeletal muscles. In this study on eight dogs it was found that the reaction persisted after ligating the portal vein but was lost when the hepatic artery also was tied.—R. G. H.

Sensitiveness of adrenalectomized rats to certain toxic substances. Crivellari (C. A.), *Am. J. Physiol. (Balt.)*, 1927, **81**, 414-421.

In a series of studies on more than 100 experimental animals and controls it was found that two or three weeks after adrenalectomy albino rats are more sensitive to the toxic action of potassium cyanide (1:12.5), nicotine (1:1.57), acetonitril (1:100) and histamine (1:12.5). This hypersensitiveness disappears for nicotine 68 days after the operation and is diminished for potassium cyanide 52 days after extirpation.—R. G. H.

Effects of epinephrin and of sympathetic stimulation upon skeletal muscle. Hartman (F. A.), Evans (J. I.) & Walker (H. G.), *Am. J. Physiol. (Balt.)*, 1927, **81**, 482.

It is possible to observe the skeletal muscle of the cat under the high power of the microscope by transmitting light to the muscle through a glass rod. In this way individual muscle fibers and the capillary circulation may be studied, provided a thin muscle is used. So far the sartorius muscle has proven the most satisfactory. Epinephrin in small amounts (0.4 cc., 1:100,000) causes new capillaries to open and capillaries already open to dilate. Venules appear to react in a similar fashion. A striking change appears in the muscle tissue itself. First, it becomes more translucent. Then with larger doses this effect not only becomes more marked but the muscle fibers stand out more clearly and the cross striations which may not have been visible before are easily seen. The muscle fibers also begin to twitch transversely. With the larger doses, the dilatation of capillaries may increase to a certain point beyond

which constriction begins to appear. In very young kittens epinephrin even with small doses causes constriction of the capillaries instead of dilatation. If the nerve is cut to a muscle and time is allowed for degeneration (in adult cats) epinephrin even in large doses causes only dilatation of the capillaries, venules and arterioles. But with the larger doses the veins and arteries become constricted. Stimulation of the sympathetic chain in the lumbar region by rapidly repeated induction shocks causes only dilatation of the capillaries and venules. We have not observed constriction from such stimulation however the rate or intensity of the shocks were varied. Very weak stimulation makes the field more opaque. As the strength of stimulation increases a point is very soon reached which causes the field to become much brighter. This is accompanied or sometimes preceded by very fine and extremely rapid vibration of the muscle fibers. The vibration soon changes to twitching resembling that produced by epinephrin. The twitching produced by chemical stimulation, as drying, is entirely different from that resulting from epinephrin or sympathetic stimulation.

—Author's Abst.

Cerebral circulation. Howe (H. S.) & McKinley (E.), Arch. Neurol. & Psychiat. (Chicago), 1927, 18, 81-86.

The capillaries of the surface of the brain were studied with a binocular microscope. It was observed that injections of from 1 to 3 cc. of 1:1,000 epinephrine hydrochloride solution did not cause any perceptible change in the size of any of the cerebral vessels in cats and rabbits. There was an acceleration of the circulation, and after doses of from 3 to 5 cc., spontaneous hemorrhages were seen. Hypodermic injections of epinephrine hydrochloride in frogs caused dilatation of the cerebral arterioles, which were at first so great that there was momentary cessation of the circulation. It was resumed again in a few moments and in some of the connecting vessels the direction of the flow was reversed. The authors did not observe any effect after the injection of 1 or 2 cc. of pituitary extract, either under normal conditions or when the arterioles were contracted by the faradic current or dilated by histamine.—R. G. H.

Adrenal auto-transplantation. Ivy (A. C.) & Oldberg (E), Am. J. Physiol. (Balt.), 1927, 81, 488.

A method has been evolved by which a functioning adrenal has been transplanted with part of its original blood supply running to it by means of a pedicle, into the omentum. The left adrenal is first mobilized and surrounded by a cape of omentum, the adrenal vein and all other vessels than those entering the inferior pole, being ligated. At a subsequent operation, the right adrenal is removed. Such dogs have lived in apparent health for a period of two weeks,

at which time they were subjected to further operative procedure. Other animals have at the time of this writing, been living in evident good health for sixteen days on such a pedicled transplant, with the right adrenal absent. The "transplant" itself has been present over six weeks in the last mentioned animals. Histologic studies of the transplants in six of the animals, show that at least some anatomically normal tissue may be expected. Other areas show varying degrees of degeneration which seems to be selective with respect to the medulla. The vessels contain blood and there is some evidence of formation of new blood supply from the omentum.—Authors' Abst.

Studies on the hemodynamic action of subcutaneously injected epinephrin. I. Some conditions under which hypodermically administered epinephrin gives a pressor effect. Luckhardt (A. B.) & Koppányi (T), *Am. J. Physiol. (Balt.)*, 1927, **81**, 436-451.

In a striking and well controlled series of experiments on small dogs it was found that subcutaneous injection of adrenalin evokes a pressor effect provided the area is massaged. The rate of appearance, magnitude of the response and its character are rather similar to those reported for moderate intravenous doses under anesthesia. Profound anesthesia (ether, barbitol-Na, and paraldehyde) militate against the occurrence of a pressor effect; whereas light paraldehyde anesthesia (or simply a profound morphine analgesia) and peripheral vasodilatation (effect by local injection of NaNO_2 or inhalation of amyl nitrite) lead to an early appearance of the pressor effect and a response of great magnitude. Data are presented showing that the intravenous injection of small quantities of ether, paraldehyde, barbitol-Na, depress the pressor effect obtained from the intravenous injection of adrenalin as well as the effect from massage of an adrenalized area as well. The fact that an increased response from massage can be obtained following a period of rest suggests that the oft-repeated massage with pressor effect leads to a depression (fatigue) of the peripheral end organ. In the dog, at least, adrenalin injected subcutaneously remains undestroyed for a very long time. In spite of numerous pressor effects obtained as a result of the massage of the adrenalectomized area a saline solution extract made 9½ hours following the injection of 3.0 cc. adrenalin gave, when injected intravenously, a very marked pressor effect.—R. G. H.

Splenic constriction caused by muscular metabolites. A double mechanism, nervous and adrenal (Constricción esplénica provocada por los metabolitos musculares. Doble nervioso y adrenalínico mecanismo). Molinelli (E. A.), *Rev. Soc. Argent. Biol.*, 1926, **2**, 130; *Compt. rend. Soc. de biol. (Par.)*, 1926, **95**, 821.

Metabolic products, produced during muscular tetanization.

cause a definite, prolonged contraction of the spleen by a double mechanism; a direct nervous one (stimulating the vaso-constrictor centers); the other humoral (increasing adrenal discharge). The experiments were made on dogs, employing Tournade and Chabrol's method of adreno-jugular anastomosis. When tetanizing the hind legs of the donor, the pressure of the receiver was either not modified, or else slightly raised, but the spleen contracted clearly and for rather a long time, sometimes for 10 minutes. There was no contraction of the spleen when the splanchnic nerves of the donor's adrenal glands were previously cut, which shows that the increase of adrenalin is of central origin. The nervous mechanism independent of adrenalin is proved by the fact that muscular effort of a denervated leg produces contraction of the spleen in a dog without adrenal glands.—Author's Abst.

Influence of normal adrenalin on arterial pressure and glucemia
(Papel de al adrenalina normal sobre la presión arterial y la glucemia). Molinelli (E. A.), Rev. Soc. Argent. Biol., 1926, 2, 218; Compt. rend. Soc. de biol. (Par.), 1926, 95, 1084.

Experiments were made on dogs, transfusing the adrenal blood of the donor, A into the jugular of the receiver, B (method of adreno-jugular anastomosis of Tournade and Chabrol). The effects of the transfusion observed in the recipient were: progressive rise of arterial pressure, increase of amplitude of heart-beats, acceleration of the denervated heart and contraction of the spleen. The blood sugar level, which habitually tends to be diminished in chloralosed dogs, was the same or a little raised, less than 0.25 per 1.000, when the dog received the adrenal blood of the donor.

—Author's Abst.

Influence of the variation of arterial pressure due to bleeding or transfusion upon adrenal secretion (Influencia de las variaciones de la presión arterial por sangría y transfusión sobre la secreción de adrenalina)... Molinelli (E. A.), Rev. Soc. Argent. Biol., 1926, 2, 200; Compt. rend. Soc. de biol. (Par.), 1926, 95, 1081.

The experiments were made on chloralosed dogs employing Tournade and Chabrol's method of adreno-jugular anastomosis. The donor's hypotension by sudden bleeding from the femoral artery of 2 to 3 per cent of its weight, caused a slight increase of adrenal discharge, while in the recipient there was increase of arterial pressure, acceleration of the denervated heart and contraction of the spleen. The donor's hypertension by a fast venous injection of physiological solution produced decrease of adrenal discharge during some minutes, which in the receiver corresponded to diminution of pressure and number of beatings and dilatation of the spleen. To restore the initial level of pressure, variations of adrenal secretion

act together with vaso-motor nervous system which is the main regulating factor.—Author's Abst.

Virtual adrenalin (L'adrénaline virtuelle). Mouriquand (G.) & Leulier (A.), *Presse Méd. (Par.)*, 1927, **35**, 819-820.

The authors had previously shown that adrenal glands of guinea pigs analyzed immediately after death contain considerably less detectable adrenalin than after 24 hours desiccation over sulphuric acid. The same was found to be true in case of glands from cattle, horses, sheep and swine as well as of guinea pigs showing avitaminosis and those treated with diphtheria toxin.—R. G. H.

The relief of itching by epinephrin in certain cases of infantile eczema. Pilcher (J. D.), *J. Am. M. Ass. (Chicago)*, 1927, **89**, 110-111.

In about three-fourths of a small series of cases Pilcher found that adrenalin gave the infants marked relief. The drug was administered hypodermically in doses of 0.1-0.3 cc. of 1:1000 solution.
—R. G. H.

The effect of adrenalin on phosphorus partition in muscle. Sacks (J.), *Am. J. Physiol. (Balt.)*, 1927, **81**, 276-279.

A study was made on white muscle from rabbits killed with chloroform, incubated in sodium bicarbonate solution. Control samples were treated immediately with trichloroacetic acid. Phosphorus partition was determined and lactacidogen then calculated. It was found that enforced inactivity results in a synthesis of the inorganic phosphates normally present in striated muscle into lactacidogen. Adrenalin produces a marked hydrolysis of lactacidogen, with the formation of an equivalent amount of phosphoric acid. This action of adrenalin is independent of the carbohydrate reserve of the animal.—R. G. H.

A method for collecting the blood from the suprarenal gland in the dog, without fastening, narcotizing, laparotomy or provoking any pain. Satake (Y.), Sugawara (T.) & Watanabé (M.), *Tohoku J. Exp. Med. (Sendai)*, 1927, **8**, 501-534.

A method for collecting the blood from the adrenal glands of the unanesthetized, quiescent, dog is described. The blood is collected by means of a lumbar route operation, the field of which is desensitized by the destruction of the corresponding dorsal roots, and without fastening, narcotizing, laparotomy, or evoking any pain. The blood was assayed by the rabbit intestine method. The spontaneous liberation of epinephrine was found to amount on an average to 0.00003 (for the left), 0.00004 (for the right) mgm. per kgm. per minute, or 0.00007 mgm. for both glands. This output is of a quite different order from that obtained by the cava pocket

method in the non-anaesthetized, de-afferented dogs as well as in the anaesthetized, normal dogs, as previously reported. The striking smallness of the epinephrine liberation shown, taken by this method, is due to actual low concentration of epinephrine in the suprarenal vein blood. By some experiments with the non-anaesthetized, de-afferented, but fastened, dogs, it was also definitely demonstrated that the preparing of the cava pocket induces a remarkable exaggeration of the epinephrine output. By the use of anaesthesia this difference becomes much reduced, and finally it disappears completely when sufficiently deep anaesthesia is established.—R. G. H.

The bactericidal action of the serum following injections of adrenalin. Smith (G. H.), *J. Immunol. (Balt. & Cambridge [Eng.])*, 1926, **12**, 205.

The author reports his studies on the influence of adrenalin upon the bactericidal action of blood serum in rabbits. The capacity of normal rabbit's serum to kill typhoid bacteria before and at varying intervals after the injection of adrenalin was compared. The sera were tested by the looped pipette method for their bactericidal effect against eighteen-hour broth culture of *B. typhosus* of known strain. Injection of adrenalin by the intraperitoneal or subcutaneous route in doses of 0.5 to 2 cc. resulted in an increased capacity of the sera to kill bacteria. Larger doses of adrenalin produced an opposite effect. The response appeared within thirty minutes after the injection and reached its maximum within about two hours, following which the potency of the serum gradually approached normal and approximated the original values within about twenty-four hours. Following daily injections of adrenalin the augmentation of the bactericidal response of the serum gradually lessened, indicating, in the author's opinion, either exhaustion of the reacting mechanism or acquired tolerance to adrenalin. The increased bactericidal action was not of specific nature, as far as a particular organism is concerned. The author points out that the mechanism involved in the bactericidal action is not clear. He indicates that it is not referable to a blood concentration or to a mobilization of the known antibodies.—S. Shapiro.

Effect of stimulation of the sensory nerves upon the rate of liberation of epinephrine from the suprarenal glands. The third report. Sugawara (T.), Watanabé (M.) & Saito (S.), *Tohoku J. Exp. Med. (Sendai)*, 1926, **7**, 1-79; *Abst., Biol. Absts.*, **1**, 471.

The cava pocket method was used for collecting the suprarenal vein blood. The epinephrine concentration was estimated by the rabbit intestine strip method and, in one case, the denervated pupil method. In control experiments cava pocket specimens were successively collected in anesthetized cats (urethane or ether) and dogs

(ether) and one non-anesthetized, de-afferented dog. The epinephrin output per minute was fairly uniform for each individual, but different for different individuals; it varied with depth of narcosis. In anesthetized cats (urethane or ether) and dogs (ether) electric stimulation of the median nerve augmented the epinephrin output in about half the cases. The rate of output during the stimuli periods was 2-3 times that in the non-stimulation periods. Increased rate of output was caused chiefly by that of the epinephrin concentration. The augmenting effect of stimulation was, as a rule, detected under light anesthesia. In all the dogs in which the dorsal spinal roots from IV thoracic to the II lumbar were previously cut on both sides, the sensory stimulation definitely called forth the augmentation, in striking contrast to the experiments under narcosis. The rate of output during the stimulation was 2-5 times that in non-stimulation stages. Narcosis inhibits partially or totally the reflex output of epinephrin.—Authors' Abst.

Epinephrine content of the suprarenals of thyroidless rats. Sun (T. P.), *Am. J. Physiol. (Balt.)*, 1927, **81**, 509.

Male and female albino rats were thyro-parathyroidectomized at 100 days of age. When 150 days old they, and their litter mate controls of the same sex and habitat, were killed by ether. The suprarenals were removed from both tests and controls, and the epinephrin content determined according to Folin, Cannon and Denis, modified to suit the material. It was found that in 10 of the 15 males, and in 10 of the 16 females, the epinephrin content per gram of suprarenal substance was higher in the glands of the thyroidless than in those of the control rats. The average increase was 24 per cent in the males and 32 per cent in the females. This finding is consistent with the fact that thyroid deficiency tends to produce cortical shrinkage with consequent increase in relative amount of medullary tissue. This alteration in the proportion of medulla to total gland weight may be the chief cause of the increment, or it may be that the lowered bodily activity of the thyroidless animals is also a participant in the observed reaction.

—Author's Abst.

Observations upon the serum calcium after adrenalectomy. Taylor (N. B.) & Caven (W. R.), *Am. J. Physiol. (Balt.)*, 1927, **81**, 511-512.

The removal of both adrenals produced a decided rise in the serum calcium within 3 to 5 hours after the operation. Both adrenals were removed at one operation by the abdominal route. The rise in the calcium varied in different animals from 10 to 40 per cent of the normal. The operation was performed upon some 36 cats, 32 of these (86 per cent) showed the rise. Only four dogs were operated upon; all of these showed a pronounced rise from 12.0 to 15.6.

mgm. in one case and from 11.0 to 14.8 mgm. in another. Control experiments in which other organs such as the alimentary canal, kidneys and spleen were removed had no effect upon the serum calcium. Anesthesia was found to have no effect; a decapitated animal in which the adrenals were removed after the effects of the anesthetic had passed off, showed the usual rise. Tying the adrenal veins had the same effect upon the calcium as adrenalectomy. Removal of one adrenal and freeing the other, but leaving its blood supply intact, was without effect; there was no change in the calcium. Destruction of the glands by crushing had the same effect as complete removal. In most cases there was a rise in blood concentration accompanying the hypercalcemia; but the increase in blood concentration which was indicated by the hemoglobin estimations, was insufficient in degree to account for the increase in serum calcium. In all cases the percentage of hemoglobin rise was much less than the percentage of calcium rise, and in some the calcium rise was not associated with any increased blood concentration whatever. Parathyroidectomized animals showed the calcium rise after adrenalectomy, provided the calcium, as a result of the parathyroid removal, had not fallen to the tetany level. If the calcium was depressed to this level (5 to 6 mgm.) adrenalectomy had much less effect in causing it to rise. In most cases there was no rise at all. This suggests that adrenalectomy affects the calcium level only when there is some parathyroid tissue present. Removal of one adrenal and the medulla of the other was without effect upon the serum calcium. Extracts prepared from the cortex of ox adrenals depressed the serum calcium in rabbits from 15 to 30 per cent.

—Authors' Abst.

Morphin intoxication in adrenalectomized rats. Torino (A.) & Lewis (J. T.), *Am. J. Physiol. (Balt.)*, 1927, **81**, 405-413.

Healthy rats, well fed and protected from cold, survive double adrenalectomy in a large percentage of cases. Death, when it occurs, is seen within the first five days following operation. Adrenalectomized rats, two weeks after operation, succumb in large numbers (69.2 per cent), to 0.04 mgm. per gram morphin chlorhydrate, a dose one-tenth of the lethal dose for normal rats. Protection from cold, by keeping the injected animals at 30°C., does not alter these results. Five weeks after adrenalectomy rats are still hypersensitive, though in a lesser degree; 0.08 mgm. per gram kills more than half the number injected. Hyperglycemia is observed in normal rats injected with 0.04 mgm. per gram morphin chlorhydrate. Hypoglycemia is seen when 0.3 and 0.4 mgm. per gram are given. Two weeks after adrenalectomy 1.04 mgm. per gram produces hypoglycemia in rats. Hyperglycemia in this condition is seen when only 0.01 mgm. per gram is injected. Repeated glucose injections do not increase tolerance for morphin in normal rats.—Author's Abst.

Neurocytoma of the left suprarenal gland with metastases to the liver, skull and bones. Sturtevant (C. N.) & Kelly (T. C.), *Am. J. Dis. Child.* (Chicago), 1927, **33**, 590-597.

A case is reported of a five year old girl with a neurocytoma of the left suprarenal gland with metastases to the skull, dura, ribs, vertebrae, right innominate, the right femur and the liver. Tumors of the orbit with ecchymosis of the eyelids and proptosis in infants and young children should arouse the suspicion of metastases from a suprarenal growth.—M. B. G.

The effect of the internal secretions and temperature on the metabolism of amino acids and simple sugars by animal cells. Burge (W. E.), Estes (A. M.), Wickwire (G. C.) & Williams (Maude), *Am. J. Physiol.* (Balt.), 1927, **81**, 468-469.

The internal secretions used in this investigation were insulin, thyroxin, adrenalin and pituitrin and the sugars dextrose, levulose and galactose. The amino acids used were glycocoll, tyrosin, nor-leucin, iso-leucin, cystin and a mixture of the naturally occurring amino acids, aminoids. Benedict's method was used for making the sugar determinations and Van Slyke's and Sørensen's for the amino acid determinations. Large quantities of paramecia were collected, washed free of debris by centrifugalization and measured in centrifugalizing tubes which were graduated in cubic centimeters. Paramecia sugar preparations were made with 5 cc. of paramecia in 100 cc. of 0.1 per cent sugar solutions. Amino acid and aminoid paramecia preparations were made with 5 cc. of paramecia in 0.3 per cent solutions of these materials. Various amounts of insulin, thyroxin, adrenalin and pituitrin were added to these preparations and sugar determinations were made immediately and subsequently at certain intervals. Paramecia use the three simple sugars dextrose, levulose and galactose. Insulin increases the utilization of all three of these sugars, just as it does in the higher animals. Pituitrin also increases the utilization of these sugars, while thyroxin decreases it. Small amounts of adrenalin increase and large amounts decrease the sugar metabolism of these organisms. Paramecia use the amino acids and the aminoids, but not nearly so rapidly as they do the sugars. The addition of insulin and pituitrin have no effect on the metabolism of the amino acids, while adrenalin and thyroxin increase it slightly. Paramecia metabolize practically no sugar at 0°C., and the metabolism is increased with a rise in temperature.—Authors' Abst.

Disturbances of humoral equilibrium. A new vascular-endocrino-automatic complex accompanied by cylindruria. Mikulowski (V.), *Arch. Pediat.* (N. Y.), 1927, **44**, 356-368.

The author describes a syndrome in a boy of 13 years which he thinks was fundamentally essentially endocrine. This boy had been

vomiting on and off for a period of six years he was very much undernourished because of war experiences, and also exceedingly nervous. For two months previous to observation his vomiting attacks were accompanied by abdominal pains, weak pulse and tonic muscular contractions which were typically tetanic in character. Trousseau's, Chvostek's and Weiss's signs were all positive. The urine showed albumin at times and hyaline and granular casts. It is considered that the patient presented a vagotonic type, based on positive Aschner-Erben reflexes and on clinical, gastric and circulatory symptoms, as well as bradycardia, bradypnea, slow circulation, hypotension, asthenia and excessive fatigability. He also presented Martinet's complex of high blood viscosity and low blood pressure, which usually is considered a symptom of endocrine insufficiency. The mechanism of this probably lies in the undernourished endocrine glands producing diminished secretion, which again augments the hypoxemia, thus leading to a vicious circle. Two weeks of thyroid treatment restored normal metabolism, and after two months the patient was discharged.—M. B. G.

Abnormal growth in a girl. Sutton (L. R.), Arch. Pediat. (N. Y.), 1927, 44, 109.

An 11 year old girl was 162.5 cm. tall, weighed 47 kilos and had a basal metabolism rate of 9 plus. Her father and a brother were also tall. Her mentality was above that of her age. While unusual symmetrical growth does not necessarily imply disease, unusual height associated with a symmetry points to giantism. Under treatment of thyroid and ovarian extracts, there was an apparent cessation of growth.—M. B. G.

The endocrine glands of rats in parabiosis. Pighini (G.) & de Paoli (M.), M. J. & Record (N. Y.), 1926, 124, 353-358; 399-404; 474-475.

The authors have had the best success by uniting the animals by the thigh muscles and skin. The first effect noted was intoxication. This occurred irrespective of sex of the pairs, but was greater when they were of opposite sex. Ten of twenty pairs survived long enough and in sufficiently good health to justify reporting. One or both of the pairs usually died within a few days, but one survived until killed on the 165th day. Parabiosis of mature rats of opposite sex induced sterility. In case of young rats the male attained fertility but soon lost it. The thymus and testes showed atrophy. The ovaries showed follicular atresia and depletion of the lutein cells with ultimate hypertrophy of the interstitial cells. These gonadal modifications are regarded not as hormone but as toxic effects. The adrenals showed hypertrophy of the medulla and depletion of cortical lipoids. The anterior lobes of the hypophysis showed congestion and accumulation of basophilic cells. The islands of Langerhans were hypertrophied.—R. G. H.

Arteriosclerotic dementia with gynecomastia. Softening of the striatum without choreo-athetotic symptoms. Urechia & Mihalescu, Tr. Soc. de Neurol. de Paris. December 2, 1926; Arch. Psychiat. & Neurol. (Chicago), 1927, 17, 841-842.

A vagabond, aged 50, presented mild achondroplasia and cardiac hypertrophy with aortitis and arteriosclerosis. The pulse rate was 56. The pupils were normal; lumbar puncture gave negative results, and the blood Wassermann reaction was negative. There were gross memory defects, indifference, apathy, lack of attention and confabulation. In July, 1924, there was a slight stroke, followed by flaccid paralysis of the right upper limb and loss of tendon reflexes. Six days later, the reflexes returned and became exaggerated. The patient could use the paralyzed limb slightly. About a month after the stroke there was manifest symmetrical hypertrophy of the breasts, and on palpation they seemed to contain glandular tissue. The testes were atrophic. The dementia had progressed to complete apathy. The patient wasted rather rapidly, could hardly stand, and had anarthria and paresis of the palate. In September, two months after the first stroke, he was found in coma with dilated, rigid pupils, and died four days later. At necropsy the calvarium was 15 mm. thick in places; the meninges were thickened; the brain was atrophic, especially in the frontal portions and more so on the right. There was a small subcortical softening in the lower third of the ascending frontal convolution. The basilar arteries were sclerotic. The left putamen was the seat of infraction which affected the external capsule, claustrum and part of the caudate nucleus. The internal capsule and globus pallidus were not involved. In the base of the brain the lesion extended close to the area of Reichert and the infundibular region. The testes and thyroid were small and sclerotic. The mammae were as large as small oranges and contained connective tissue and a little glandular substance. Microscopic examination of the testes revealed marked fatty degeneration with rare spermatozoa. The interstitial gland was poor in lipochrome, and many of the cells were empty. In the mammary gland there were several acini with many rows of cells. In the brain there was pronounced fatty degeneration in various locations, with chronic and intense lesions. The neuroglia were hyperplastic, and there was much sclerosis and hyaline degeneration of the vessels, especially of the small vessels of the cortex, as described by Alzheimer. The most interesting feature in the case was the gynecomastia. This dystrophy was related to an evident atrophy of the testes. It has been noted equally in those affected by hypothyroidism, acromegaly, hypopituitarism and status thymicus. The atrophy and the secondary hypertrophy of the breasts followed the stroke within a few days. The softening, however, did not involve the nuclei of the infundibular region or the Reichert nucleus and was only on one side. An indirect relationship between the tuber

and gynecomastia is probable. It has been shown that alteration of this region is capable of producing testicular atrophy and the adiposogenital syndrome. In this case the severest lesions were found in the supra-optic nuclei. In another case, a report of which was published with Elekes, and which also presented diabetes insipidus, the nuclei also presented severe changes. We should not affirm, however, that changes in these nuclei led to interstitial atrophy.

On the effect of the ovarian hormone in producing pro-oestrous development in the dog and rabbit. Asdell (S. A.) & Marshall (F. H. A.), *Proc. Roy. Soc. (Lond.)*, S.B., 1927, **101**, 185-192.

Injections of the alcohol soluble fraction of follicular fluid extending over ten days produced typical pro-oestrous changes in the uterus of the normal bitch during the period of anoestrus (sexual quiescence). The vaginal epithelium grew and became stratified and the outer layers became cornified. Injections extending over seven days in the spayed rabbit induced pro-oestrous conditions in the uterus and vagina. The vaginal epithelium remained single layered, but the surface was thrown into complex folds. Neither swelling of the vulva nor mating reactions were noted in the injected animals. There was no apparent effect upon the ovaries of the bitch.—E. A.

Testicular grafts in young goats (*Greffes testiculaires de jeunes beliers. Rapide resorption des greffons*). Baloget (L.), *Compt. rend Soc. de biol. (Par.)*, 1927, **96**, 104-106.

The author reports histological findings in testicular grafts in young goats. The receptor was two years old, the donor between twelve and eighteen months. Two pieces of testis, each 35 mm. by 15-17 mm. and 10 mm. thick, were imbedded on the tunica vaginalis. After thirty days one graft was recovered. It was then 16 mm. long and 8 mm. thick. It presented an aspect of necrosis. There were no nuclei of seminiferous or Sertoli cells visible. No interstitial cells were found. The grafted tissue was organized by an ingrowth of fibroblasts. The second graft was completely reabsorbed sixty days after implantation.—Robert M. Oslund.

Changes in the ovary of the mouse following exposure to X-rays.

Part II.—Irradiation at or before birth. Brambell (F. W. R.), Parks (A. S.) & Fielding (U.), *Proc. Roy. Soc. B. (Lond.)*, 1927, **101**, 95-114.

It was found that exposure to x-rays at this time is followed by degeneration of oocytes and follicles. Later two successive proliferations of the germinal epithelium occur in the form of cords. Follicles were completely absent. It is concluded that the cells of the first proliferation are mainly responsible for the production of the

ovarian hormone responsible for oestrus. In many cases where the epithelial cords differentiated into luteal like tissue, cycles were absent or had ceased at least 36 days before the animals were killed.
—E. A.

Effect of washing with physiological saline on spontaneous rhythm of uterus (*Influence du lavage par une solution physiologique sur le rythme spontané de l'utérus*). Brouha (L.) & Simonnet (H.), *Compt. rend. Soc. de biol. (Par.)*, 1927, 96, 154-155.

In the uterine muscle of the rat or cavy, irrigation with Ringer's diminishes or abolishes the rhythmic contraction. The rhythm may be restored by use of follicular fluid or extracts.—E. P. Durrant.

Uterine contractility, oestrous and folliculine (*Uterine contractilité, oestrus et folliculine*). Brouha (L.) & Simonnet (H.), *Compt. rend. Soc. de biol. (Par.)*, 1927, 96, 155-156.

Washings from the uterus (rat) at oestrous contain substances capable of setting up rhythmic contractions in quiescent uterine muscle and bringing on the vaginal phenomena of oestrous.—E. P. Durrant.

Influence of ovarian function on basal metabolism. Heyn (A.), *Arch. f. Gynaek. (Berl.)*, 1927, 129, 760; *Abts., J. Am. M. Ass.*, 89, 72.

Basal metabolism was not found to be affected by the menstrual cycle in healthy women or by dysmenorrhea. High grade ovarian insufficiency (primary amenorrhea) was accompanied by a decrease of about 10%. The decrease was slight and inconstant in the lower grades of ovarian insufficiency. In about 25% of the cases of hemorrhagic metropathy, the basal metabolism was increased more than 10%. In about 50% of women with myoma, it was increased from 10 to 20%. Castration was followed in 25% of the cases by a distinct decrease, which, however, proved temporary, being present two to three months after the castration, but disappearing after six to nine months. In the other cases the rate was normal. In women in the natural menopause, the rate varied in both directions; in some cases it rose as much as 10%. By ovarian preparations it was possible to raise the metabolic rate of castrated women with decreased metabolism to normal, but not above normal. Heyn regards the influence of the ovaries on metabolism as secondary, through its action on thyroid function. In amenorrhea he sees the result of insufficiency of the endocrine system, not of one gland alone.

Studies on vigor. IX. The effects of ovarian extirpation on fatigability of muscle in the rat. Miley (H. H.), *Am. J. Physiol. (Balt.)*, 1927, 81, 500.

Studies on female albino rats by the revolving cage method have shown that spaying results in a marked decrease in voluntary activity. Available data offers little in the way of explanation of such findings. Believing that the field could be narrowed somewhat by a quantitative study of the fatigability of nerve-muscle preparations, *in situ*, a comparative study was made of the strength and fatigability of the gastrocnemius muscles of ovariectomized and normal rats. The animals were anesthetized with amytal, which was injected subcutaneously so that uniform and prolonged anesthesia could be obtained. The muscles were stimulated through their motor nerves at one second intervals, using break shocks only. It was found that ovariectomized animals gained weight more readily than their controls, and the weights of the individual muscles were greater in the spayed animals. The absolute strength per gram of muscle averaged 40 per cent greater for the controls than for the experimentals. The proportion of gastrocnemius weight to total body weight averaged the same in each group. The total work performed by the ovariectomized animals was only 33.6 per cent of that done by the controls. This agrees well with the decrease in voluntary activity following spaying. The average daily activity of the castrated males in Gans and Hoskins' experiments was 2298 revolutions, while that for the spayed females in these experiments was 2651 revolutions. A comparison of the ergographic and revolving cage records shows that the best control did 2,663,900 gram-centimeters of work correlated with a daily activity of 10,091 revolutions. The best experimental did 893,600 gram-centimeters of work and had a daily activity record of 683 revolutions.—Author's Abst.

On the properties of the gonads as controllers of somatic and psychological characteristics. IX. Testis graft reactions in different environments (rat). Moore (C. R.), *Am. J. Anat.* (Balt.), 1926, 37, 351-416; Abst., *Biol. Absts.*, 1, 474.

A report on the recovery and study of more than 100 testis grafts, persisting for 1-6½ months after transplantation. The relative persistence of grafts was: normal males 56%; castrated males 79%; normal females (mated and unmated) 62%; spayed females 95%; grafts in scrotum of castrated males 38%; gross recovery from all groups combined 59%. Entire young testes with attached epididymis were used. The variable tissue reaction in the persisting grafts involves apparent hypertrophy of interstitial cells and lack of it; spermatogenesis and lack of it, without any specific correlation of graft and physiological state of the host animal. Grafts made in the scrotum of castrated males produced spermatozoa; the results support the author's recent contentions that the scrotum functions as a local thermoregulator for the testes, and that such a regulatory function is essential for spermatozoon production. General consid-

erations, and deductions from testis transplantation, graft reactions, and effectiveness of grafts are discussed. A literature review is included.

Attempt to purify a morphogenetic ovarian hormone (*Essais de purification d'une hormone ovarienne a action morphogene*). Lipschutz (A.), Vesnjakov (R.), Tuisk (R.) & Adamberg (L.), *Compt. rend. Soc. de biol. (Par.)*, 1926, **94**, 738.

After routine extraction of follicular fluid, further treatment with water and ether gives a very active substance. A short oestrous reaction in the spayed mouse is reported from two successive injections of aqueous solution, the minimal effective dose being 1/50,000 mgm. Aqueous solutions lose their activity in a few days.—E. A.

Basal metabolism in the rat during the oestrous cycle. Lee (M. O.), *Am. J. Physiol. (Balt.)*, 1927, **81**, 492-493.

The basal metabolic rate was determined at different stages during the oestrous cycle in eight female albino rats from four to seven months of age. At least one complete cycle was followed in each rat and from one to twenty determinations were made in each stage. A modification of the gravimetric method of Haldane was used. Respiratory quotients were determined during two complete cycles in two rats and found to be nearly constant for fasting animals; thereafter an R.Q. of 0.75 was assumed. Body surface was computed from the formula $S = kW^{\frac{2}{3}}$, in which S is the body surface in square centimeters, W is body weight in grams, and k is 11.36. The heat production per square meter of body surface per day was found to show consistent variations from the general mean only toward the end of stage V (dioestrus) and at the beginning of stage I (pro-oestrus). At that time an average increase amounting to approximately 12 per cent of the general mean was noted. This increased heat production appeared in the last ten hours of the dioestrus and gradually disappeared in the early part of the pro-oestrus. During none of the other stages of the cycle was there any significant change in the heat production. Even during stage II (oestrus) which is characterized by a marked increase in excitability and voluntary activity, the average heat production was below the general mean. These results are interpreted as indicating that the oestrus-producing hormone of the ovary is not primarily a metabolic stimulant. The increased heat production in the rat toward the end of the dioestrus seems to be comparable to a slight increase reported in women at menstruation, and is ascribed to an effect of an ovarian hormone on the thyroid. The metabolic rate was determined in these same rats following ovariectomy, at intervals over a period of two months. The mean of these determinations was about 10 per cent below the mean of the determinations before removal of the ovaries.—Author's Abst.

The effect of the follicular hormone on old albino rats. Slonaker (J. R.), *Am. J. Physiol. (Balt.)*, 1927, **81**, 325-335.

Fifty-seven experiments were tried on rats varying in age from 538 to 971 days. Some of the rats were normal, others spayed or hysterectomized. Cornified cells were found in vaginal smears long after the donors had passed the menopause, or had ceased to show marked increases in voluntary activity and mating activities. These cells often persisted for from one to three or four days. It appeared that oestral changes in the vaginal mucosa can be incited by a smaller dose of the hormone than that required to excite mating activities. One or two injections of fresh follicular hormone had little or no effect in modifying oestral rhythm, or inducing mating in rats nearing the menopause. In older animals it was found that copulation may occur if the injection coincides with a normal appearance of cornified cells. One or two injections did not induce oestral changes in the vaginal mucosa of ovariectomized rats 600 days old. Nine injections caused such changes in ovariectomized rats 719 days of age. These changes appeared but once and lasted from two to four days. Three to nine injections of the follicular hormone seemed to be favorable for both oestral changes in the vaginal mucosa and mating in normal rats of various ages. The results indicate that the hormone does not prolong the productive sexual life of the animal by inciting ovulation but that it may stimulate mating activities. As a result of the hormone injections the majority of the animals showed a reduction in food consumption and spontaneous activity accompanied by an increase in body weight. This effect was of short duration, and a return to normal in a short time usually occurred. All results indicated that the effect of the injected hormone is but transitory, lasting only a few days at the most.—R. G. H.

On the occurrence of the oestrous cycle after x-ray sterilization.

Part II.—Irradiation at or before birth. Parkes (A. S.), *Proc. Roy. Soc. (Lond.)*, S. B. 1927, **101**, 71-95.

Mice sterilized by exposure to x-rays during the week after birth later became sexually mature and experienced apparently typically oestrous cycles. Although these cycles were somewhat irregular the histologic changes of uterus and vagina were normal and mating reactions resulted in successful copulation. In some of the animals neither follicles nor corpora lutea were present, the sterile ovaries being composed of a new proliferation of tissue from the germinal epithelium. In some of the ovaries an extreme development of luteal-like tissue was correlated with absence of oestrus. The conclusion is drawn that neither follicles nor corpora are essential in the mechanism of the oestrous cycle in the mouse.—E. A.

Lactation and the glands of internal secretion (*Lactation und Drüsen innerer Sekretion*). Verdozzi (C.), *Policlín. (Roma)*, 33, 1926, Nr. 12; *Abst., Monatschr. f. Kinderh. (Leipz. & Wien.)*, 1927, 36, 88-89.

The author shows in the case of guinea pigs in lactation a limitation or restraining of the ovarian follicle, while in the behavior of the *corpus luteum* no difference exists between them and control animals. He shows further that during lactation changes occur in the thyroid of the animal; the alveoli become numerous and very large, tensely filled with colloidal material, the epithelium much flattened, in short, the picture of a strong functional activity present in the thyroid. The hyperplasia was great after 15 days' lactation, less so after 20-25 days' lactation. The explanation given for these conditions is that while lactation lasts about 30 days in the animal, the young from the 15th day are nourished with mixed food. It is stated that an inner secretion of the interstitial cells of the mammary glands affects the development of the ovarian follicle during lactation. Further, the hyperfunction in the thyroid of mother animals is connected with the mammary gland. The thyroid in young animals is not very active and the necessary thyroid hormone is supplied to them from the mother through the milk.—E. P. Durrant.

Diabetes insipidus. Blatt (M. L.) & Greengard (J.), *Arch. Pediat. (N. Y.)*, 1926, 43, 611.

A case is reported of a boy of 12 years who gave a history of polydipsia, polyuria, retarded growth and development and headaches for a duration of eight years following an attack of scarlet fever. There was also an increased sugar tolerance. Pituitary treatment was of no avail when tried under the tongue or by mouth, but when given hypodermically in doses of 1 to 2 cc. per day an improvement was noted.—M. B. G.

The hypophysis and the internal secretions of the ovary (*L'hypophyse et la sécrétion interne de l'ovaire*). Brouha (L.) & Simonnet (H.), *Compt. rend. Soc. de biol. (Par.)*, 1927, 96, 1275-1276.

Extracts of hypophysis by lipid solvents were found to contain a substance having properties identical with that of folliculin in respect to the effects on development and phenomena of the sex cycle. The authors believe their results are in favor of the hypophyseal origin of the internal secretion of the ovary, although they do not exclude the possibility of the direct action of the hypophysis on ovogenesis.—E. P. Durrant.

The expansion of frog melanophores as a biologic test of hypophyseal extracts and the influence of chloretone on the test (*Sopra l'espansione dei melanofori della rana come saggio biologico delgi*

estratti ipofisari e sull'influenza che vi spiega il cloretone). Di Mattei (P.), Roma, 1923-1927, Ed. Pozzi, p. 24.

Expansion of the melanophores in the frog, suggested as a biologic test of hypophyseal extracts, does not correspond to the pharmacodynamic characteristics of the active hypophyseal principles; in a way it gives contradictory results and has no characteristics whatever of specificity. Numerous other organs (anterior pituitary, liver, brain, thymus and thyroid), as well as many chemical substances, may provoke such a reaction. The results reported by previous investigators, who brought forward the melanophore test, were more or less vitiated by the presence of chloretone in many of the extracts used. This drug has a decided depressive action on the frog melanophores, leading to darkening of the skin. The weak points of such a "specific reaction" should make one very careful in proposing new biological tests. It is indispensable for a proponent of a biologic test to offer scientific guarantees analogous to those offered in chemical research.—G. V.

Hypopituitarism: congenital pituitary tumor; optic nerve atrophy.

Kerley (C. G.), Arch. Pediat. (N. Y.), 1927, **44**, 387-390.

A 17 year old girl first showed signs of disturbed vision between the ages of seven and eight years, and became totally blind at ten years. She was of normal mentality but showed physical pituitary disturbances, such as overweight for her height but underweight for her age, delayed menstruation, absence of secondary sex changes (axillary and pubic hair, mammary development), and external genitalia of a ten year old girl. X-ray examination of the skull showed a greatly enlarged sella turcica. The author made a diagnosis of either congenital or early pituitary tumor on the blindness, sella turcica picture and the general appearance of hypopituitarism.—M. B. G.

The rôle of the hypophysis in the initiation of labor. Van Dyke (H. B.) & Kraft (A.), Am. J. Physiol. (Balt.), 1927, **81**, 512.

Dixon and Marshal have published data which seems to prove that the intravenous injection of ovarian extracts from animals at or near term causes the appearance in the cerebrospinal fluid of an oxytocic substance, presumably liberated by the posterior lobe of the hypophysis. In this experiment the attempt was made to detect a difference in the concentration of oxytocic substance (by adding cerebrospinal fluids to Tyrode solution baths containing sensitive isolated guinea pig uteri), in the cerebrospinal fluid of patients near term and in labor 3 to 6 hours. In no instance has such an attempt been successful.—Authors' Abst.

Increased regeneration of skin due to insulin (Beeinflussung der Regenerationsfähigkeit der Haut durch lokale Applikation von Insulin). Adlersberg (D.) & Perutz (A.), *Klin. Wchnschr. (Berl.)*, 1927, 6, 108-110; *Abst., Physiol. Absts.* 12, 230.

The authors describe experiments in which ulcers of the skin were treated with insulin. Some of the ulcers were produced artificially in rabbits by the application of sulphuric acid; others were chronic ulcers in patients due to various causes. Striking results of the treatment are described. Ulcers which had been refractory for months or years became covered with epithelium within 10 days to 3 weeks. The insulin 2 cc. (40 units) was applied directly to the ulcer, which was then covered with a vaselined bandage.

Myrtillin. Allen (F. M.), *Am. J. Physiol. (Balt.)*, 1927, 81, 462.

Myrtillin is an extract of green leaves, prepared according to a method discovered and described by Wagner. Teas or powders of leaves of the myrtle family of plants have long been used for treating diabetes among the peasants in certain regions, and for technical reasons these plants are actually the best source of the material in quantity. It is called myrtillin for this reason. The chemical nature or composition is unknown; it may possibly be classifiable among the vitamins. It is non-toxic. It is entirely different from insulin and all insulin-like substances obtained heretofore from animal or vegetable sources. It is effective when given by mouth. It has no important influence upon the normal blood sugar, and never causes hypoglycemia, tending rather to prevent hypoglycemia due to insulin. Its prominent physiological properties, according to experiments in collaboration with Wagner, with doses of 0.3 to 2.0 grams per day, are as follows: It reduces the glycosuria and hyperglycemia following glucose administration (orally or intravenously) in normal animals or persons. It reduces adrenalin hyperglycemia. It accelerates oxygen consumption after carbohydrate ingestion in normal and diabetic persons, indicating a probable stimulation of the combustion. It enables totally depancreatized dogs to heal their wounds and live 4 to 6 weeks in good condition, fatal cachexia then ensuing. These dogs have marked hyperglycemia and moderate glycosuria, but on proper diet the carbohydrate balance is positive. Glycogen values may be 3 or 4 per cent in the liver, and are within normal limits in the heart. Dogs not quite totally depancreatized, retaining one-twentieth or less of the pancreas, are enabled by myrtillin to be free from glycosuria or hyperglycemia on diets containing liberal carbohydrate, and they apparently thrive indefinitely. The results in diabetic patients are more gradual and less uniform, and are to be described in later communications. Myrtillin is not a substitute for insulin, but is probably to be regarded as an accessory substance which is widely distributed in nature and

which plays a part in the carbohydrate metabolism of plants and animals. It thus has a distinct therapeutic usefulness when properly administered to selected diabetic patients.—Author's Abst.

The reciprocal action of insulin and adrenalin on the nitrogen metabolism. Aoki (K.), *Folia Endocrinologica Japonica* (Kyoto), 1927, 3, 9-10.

Experiments were carried out in nine healthy female dogs, one group of which was fed on carbohydrate-rich and the other on carbohydrate-poor diet. As soon as the animals were in nitrogenous equilibrium adrenalin solution was injected subcutaneously, and a week later the same dose of adrenalin was given together with a subcutaneous injection of insulin. In some cases, as a check, the combined dose preceded the single. In the dogs on a carbohydrate-rich diet it was found that adrenalin caused a marked decrease in the excretion of total and creatin nitrogen and acetone bodies, followed by the appearance of sugar in the urine, but no change in the output of urea, ammonia or creatinine-nitrogen. Essentially similar results were obtained with carbohydrate-poor diet. The addition of insulin lessened the adrenalin effects just specified.—From Author's Abst. R. G. H.

The utilization of dextrose, levulose and galactose by animal and plant cells, and the antagonistic action of insulin to thyroxin. Burge (W. E.) & Williams (Maude), *Am. J. Physiol.* (Balt.), 1927, 81, 307-314.

Animal cells (paramecia) and plant cells (spirogyra) utilize dextrose, levulose and galactose (when added to the culture medium). The animal cells utilize these sugars more rapidly than the plant cells. Both the animal and the plant cells utilize dextrose, levulose more rapidly than the galactose, and the dextrose more rapidly than the levulose. Insulin increases the rate of utilization of the sugars, both by the plant and animal cells. Ordinary daylight produces little or no effect on the rate of utilization of the sugars by the plant cells. Thyroxin decreases the utilization of dextrose, levulose and galactose in animal cells (paramecia), while insulin increases it. Thyroxin antagonizes the action of insulin on sugar utilization, which may be responsible for the lowered respiratory quotient and glycosuria in exophthalmic goiter, as well as in animals to which thyroxin has been given.—Authors' Abst.

Role of purification of insulin preparations in phenomena of hypoglycemia. Chabanier (H.), Lebert (M.) & Lobo-Onell (C.), *Bull. Acad. de méd.* (Par.), 1927, 97, 577.

While many insulin reactions are reported from the United States, but few seem to happen in France and the authors think

that this discrepancy may be due to the fact that American is not as closely titrated as French insulin, thus the dosage of the French product can be more closely gauged. Or, they think, there may be a difference in purification and that the reactions occur directly in proportion to the purity of the product.—H. J. J.

Effect of oral administration of sulphur on diabetic metabolism (Wirkung peroraler Schwefelzufuhr auf die diabetische Stoffwechselstörung). Foldes (E.), Ztschr. f. d. ges. exper. Med. (Berl.), 1927, 55, 615-626.

Abel and Geiling have shown that the insulin molecule contains sulphur and that the hormone loses in efficiency when the sulphur is lost. Burgi and Gordonoff found an increase in the amount of glycogen in the livers of rabbits fed with sulphur. Foldes therefore states that the sulphur in insulin bears a relationship similar to that of the iodine in the thyroid hormone and that the functional activity of insulin depends upon its sulphur content as that of thyroid does on its iodine. He found that the administration of sulphur to diabetics was followed by a total sulphur excretion of either high normal or supranormal values; that the excretion of combined sulphur salts varies, being either at, above or below normal and that percentage of combined sulphur salts is mostly below normal or at the lower border of the normal zone. Study of the blood and urine changes led him to conclude that the administration of sulphur to diabetics results, in some, in a diminution of urine sugar, of blood sugar and of ketone bodies excretion. There is a corresponding increase in sugar tolerance. On the other hand, there are some diabetics who do not react in this manner, but in whom simultaneous administration of thyroid extract and sulphur increases sugar tolerance. M. B. G.

The adrenal mechanism and the modifications of insulin action by post-pituitary extracts. Geiling (E. M. K.) & Britton (S. W.), Am. J. Physiol. (Balt.), 1927, 81, 478.

Protection against insulin hypoglycemia and convulsions in cats and dogs is shown definitely to be afforded by the simultaneous administration with insulin of extracts of the posterior pituitary lobe. Very large doses of the extract are necessary to produce this effect. If smaller amounts which nevertheless bring about extreme circulatory disturbance are employed convulsions are merely postponed. The action of superconvulsive doses of insulin (4 to 6 units per kgm. body weight) is not counteracted by very large amounts (3 cc to 4 cc.) of pituitary extract (U. S. P.). If the adrenal medulla is inactivated by removal of the right and denervation of the left gland, the protection against insulin by pituitary extract (given simultaneously) is very markedly lessened. When it is adminis-

tered in such doses during hypoglycemia, severe convulsions or all signs of muscular weakness may nevertheless be abolished and the blood sugar level may be sharply raised. Animals with the adrenal glands intact may be similarly restored, although the blood sugar percentage often remains only slightly or not at all changed near the convulsive level. Pituitary extract may therefore completely offset all symptoms of insulin shock without appreciably altering the glycemia in the general circulation. In contrast with the foregoing is the observation that pituitary extract has no apparent constant effect on the blood sugar level in the fasting normal or adrenal inactivated animal. The depression of sympathetic nervous activity by ergotamine does not affect the restorative potency of pituitary extract given during the hypoglycemic reaction. When pituitary extract is given simultaneously with insulin to either normal or medulliadrenal inactive animals, and the blood sugar has later fallen to a low level, adrenalin may abolish the apparent general reaction (weakness or convulsions), although the hypoglycemia commonly remains unaffected. The evidence establishes that there is present in pituitary extract a protective factor against insulin hypoglycemia and convulsions, and that facilitation of the action of the extract is afforded by the presence and augmented secretion of the medulla of the adrenal glands.—Authors' Abst.

Origin of the islands of Langerhans from the excretory system of the pancreas (*Le rôle du système excréteur du pancréas dans la genèse des îlots de Langerhans*). Hickel (P.) & Nordmann (J.), *Ann. d'anat. Pathol. et d'anat. normale méd. chirurg. (Par.)*, 1926, 3, 587-608.

A study was made of the formation of islets of Langerhans from the excretory ducts and centro-alveolar cells of the pancreas, based on a study of sections of three organs from men of 37, 58, and 62 years of age respectively. The authors describe the formation of islets from the walls of excretory ducts. Masses of insular tissue were seen in direct connection with the epithelium of the ducts. This method of formation of new islets is, however, less common than their development from the centro-alveolar cells. The stages of transformation from the flattened branching type of cell to secreting cells could be traced within the acinus. Later the acinar cells became flattened and degenerate, and new islands are formed by the confluence of adjacent groups of the transformed centro-alveolar cells. Direct transformation of alveolar tissue into insular tissue was not seen. In pathological cases the alveoli may differentiate and form ducts and from these islands may arise. No evidence was found of transformation of islets into acini.—M. M. H.

Growth in children with diabetes mellitus, Ladd (W. S.) & Day (C. S.), *Am. J. Dis. Child. (Chicago)*, 1926 32, 812-839.

This report is based upon a study of 34 cases of diabetes mell-

tus and one case of renal diabetes in children. All but four occurred in patients who were either overweight or overgrown or both at the onset of the disease. In two of the remaining cases the onset of the diabetes occurred after acute infection. Growth in height in children with diabetes mellitus diminishes or stops completely, depending on the severity of the case and appears to be due to lack of food. Insulin enables the patient to use sufficient food and growth follows. The optimal weight for a diabetic child is the average weight for height as expressed in the Bardeen growth curve for normal children. The optimal food intake is somewhat less than, possibly about two-thirds of, the total calories of Holt and Fales standards. The average proportions are carbohydrates 35 per cent, protein 15 per cent, and fats 50 per cent. Regularity in food intake and insulin dosage both as to amount and time administered is absolutely essential to the successful progress of the patient.—M. B. G.

Diabetes mellitus, refractory to insulin. Taussig (A. E.), Tr. Ass. Am. Physicians (Phila.), 1927; Abst., J. Am. M. Ass. **89**, 149.

A patient with progressively severe diabetes showed urticaria after injections of insulin. She went into diabetic coma and was given enormous doses of insulin, but was never entirely sugar free. One day she had 1,100 units of insulin. In patients who showed little or no drop after intravenous injections, hypodermic injections were tried with no better results. Fractional doses of 20 units hourly were also given, but this too failed to make the patients sugar free. After two months the response to insulin showed improvement and 200 units daily could be given. Finally, the insulin was brought down to 104 units daily. To find the reason for this refractory condition, 10 cc. of the patient's blood was injected into rabbits, but there was no result. Tests were then made for an allergic skin reaction without result. The urine was tested but no trace of insulin was found. The theory was considered that insulin acts as a coferment, transforming blood sugar into glycogen or lactic acid. In some persons the other constituent (muscle phosphate) may be lacking or may be present in too small amounts, so that insulin is not able to do its work.

Carcinoma of the islands of the pancreas. Hyperinsulinism and hyperglycemia. Wilder (R. M.), Allen (F. N.), Power (M. H.) & Robertson (H. E.), J. Am. M. Ass. (Chicago), 1927, **89**, 348-355.

In a human case of cancer originating in the islands of Langerhans, hourly doses of glucose were required to prevent convulsions from spontaneous hypoglycemia. When the ingestion of the necessary sugar was delayed, the blood sugar fell below 0.03 per cent. The blood phosphates fell with the sugar and rose again on

the restoration of the blood sugar. The liver functioned normally in deaminizing amino-acids and excreting bile and test dyes, but the glycogen stores proved abnormally stable to the action of epinephrine. Necropsy revealed a liver weighing 3,300 grams and containing 8.25 per cent of glycogen, carcinoma of the pancreas, and carcinomatous metastasis to the liver and lymph nodes. The cells of this cancer bore a striking resemblance to the cells of the islands of Langerhans, and alcoholic extracts made from the cancer tissue in the liver acted like insulin on injection into rabbits.—Authors' Abst.

On the alleged antagonistic action of the internal secretions of the pancreas and the thyroid. Wolfson (H.), *Am. J. Physiol.* (Balt.), 1927, **81**, 453-459.

It was found that, contrary to results of earlier studies, thyroidectomy on diabetic dogs without insulin treatment is ineffective in lowering blood sugar levels during the recorded period of survival of the animals. Urinary sugar excretion may be somewhat diminished, but the animal is never aglycosuric. The experimental procedure employed, while an improvement over the former methods, is still lacking in complete control. A state of hypothyroidism in the dog has never been completely established. Further work should be done under methods of even better control.—R. G. H.

Calcium deficiency and bone changes in experimental obstructive jaundice. Buchbinder (W. C.) & Kern (Ruth), *Am. J. Physiol.* (Balt.), 1927, **81**, 468.

Further observations of the calcium content of the blood serum of puppies with experimentally induced jaundice reveal a fairly progressive decrease, which substantiates the findings previously recorded. Although the blood serum calcium was reduced to the tetany level, no sign of increased irritability of the neuromuscular apparatus was noted. A marked osteoporotic condition with marked thinning of the cortical portions of the bone and increased fragility was a constant finding. The further striking observations were that the survival period after the induction of jaundice was much longer than that hitherto recorded for the adult animal. Growth of skeletal structures with a considerable gain in body weight was noted at the time of death. The factors responsible for the bone lysis may be the rapid growth and failure of calcium absorption in the presence of some calcium precipitating mechanism by certain of the biliary constituents. A parathyroid element is suspected of playing some rôle and the evaluation of this factor may be made possible by noting the effects of parathyroidectomy in the recently and chronically jaundiced animals, both young and adult.—Authors' Abst.

Observations on the preparation, properties and sources of the parathyroid hormone. Part I. Davies (D. T.), Dickens (F.) & Dodd (E. C.), *Bio-Chem. J. (Liverp.)*, 1926, 20, 695-702.

The serum calcium content of rabbits was found to vary within about 1 mgm. per 100 cc. throughout the 24 hours. When injected at four-hour intervals with large doses of a parathyroid preparation made by Collip and Clark's process the serum calcium content of rabbit's blood rose during the period of the experiment. The hormone yields a picrate which is insoluble in water but soluble in 70 per cent acetone, and which can be converted into a hydrochloride by Dudley's method. Active material can be extracted from the parathyroid glands by means of the acetone-picric acid process. Insulin, when administered in the same manner to rabbits as the parathyroid extract, was found to cause an increase in the serum calcium content. Pituitrin also gave a smaller rise, but when these two substances were administered simultaneously, both the calcium elevating powers and the blood sugar lowering activity of insulin were inhibited. The significance of these observations is discussed—Authors' Abst.

Effect of potent parathyroid extract on calcium balance in infants.

Hoag (L. A.), Rivkin (H.), Weigle (C. E.) & Berliner (F.), *Am. J. Dis. Child. (Chicago)*, 1927, 33, 910-925.

The influence on potent parathyroid extracts on the calcium balance was studied in seven infants: one normal, four rachitic and two with infantile tetany. The results obtained in the test periods were controlled by fore-period and after-period studies without the extract. One normal infant and three with rickets showed distinct diminution of calcium retention during the periods in which parathyroid extract was administered. The decrease did not bear a constant relation to the dosage nor to its effect on the level of serum calcium. In these cases the extract caused both an absolute and a proportional increase in the urinary excretion of calcium. One patient with rickets was given parathyroid extract daily for 25 days without producing recognizable roentgenologic evidence of either calcium removal or deposition in the radius of ulna. Two patients with infantile tetany showed a slight tendency toward increased retention of calcium during the periods of parathyroid administration. One rachitic patient with marked signs of disturbed calcium metabolism showed a more marked retention. In these cases the concentration of serum was initially low and was not markedly raised by the extract and never reached normal levels. Even though the influence of potent parathyroid extracts on the balance of calcium was not found to be uniformly unfavorable, its administration for any purpose other than immediate, temporary elevation of serum calcium should still be considered an experimental and not a routine clinical procedure.—M. B. G.

On the existence of a parathyroid hormone. Jung (F. T.), *Am. J. Physiol. (Balt.)*, 1927, **81**, 489.

The question whether the parathyroids act by detoxication or by producing a hormone is decided in favor of the latter hypothesis by the work which various investigators have done on parathyroid extracts, provided the objection can be met that such extracts might contain artifacts which are produced by the extraction processes and which perhaps accidentally simulate some phases of parathyroid function. This objection would be met by an experiment in which the whole gland, subjected to the minimum of treatment necessary to insure its death, is administered parenterally to parathyroidectomized animals. The present experiment was of that kind. White rats were parathyroidectomized and divided into three groups. The first group was untreated. Group 2 received, before parathyroidectomy, an implantation of dog or cat parathyroids, usually in the abdomen. Group 3 received, before thyroidectomy, implantations of spleen, salivary gland, or testis from cats or dogs. The rats were then studied in regard to the various manifestations of parathyroid deficiency. The results from group 1 were radically different from those given by groups 2 and 3, emphasizing the fact that group 3 were the true controls. Between groups 2 and 3 a marked difference was found, particularly in the shape of the mortality curve. Numerical data were obtained which showed that the tetany was less severe, and the ultimate mortality less, in group 2 than in group 3, and the mortality curve in group 2 exhibited a striking convexity during the first 75 hours. Since the conditions of the experiment were such as to make even temporary functioning of the implants highly improbable, the conclusion is that the parathyroid tissue, while being absorbed, liberated into the body of the recipient a material which was not species-specific, not present in the control tissues, and not a chemical artifact, which did mitigate the consequences of the parathyroidectomy, and which was probably the parathyroid hormone.—Author's Abst.

The rôle of toxins in parathyroid tetany. Larson (E.) & Elkourie (L. A.), *Am. J. Physiol. (Balt.)*, 1927, **81**, 492.

It was reported by Dragstedt and Sudan that parathyroid tetany in dogs can be controlled by oral administration of kaolin. In this experiment 100 grams of kaolin was fed daily to a series of 12 thyro-parathyroidectomized dogs. These animals were kept on a diet of kitchen scraps which consisted very largely of carbohydrates. It was found necessary in every case to resort to frequent injections of calcium salts in order to prolong the lives of the animals. In order to better compare the rapidity and severity of the tetanic attacks when relieved by intravenous injections of calcium lactate, 8 dogs were operated and the tetany controlled by this method. Analyses of the blood at the time of tetany have always shown a low value

for calcium and usually a decrease in guanidine content. Kaolin does not absorb any guanidine from 0.2 per cent hydrochloric acid solution.' From an alkaline solution there is no absorption for at least a period of one hour. The calcium content of kaolin is negligible. From these results it is concluded that kaolin does not have any decided effect in controlling tetany in thyro-parathyroidectomized dogs.—Authors' Abst.

The prevention of tetany by oral administration of magnesium lactate. Wenner (W. F.), *Am. J. Physiol. (Balt.)*, 1927, **81**, 392-403.

In ten dogs it was found that continuous oral administration of magnesium lactate (5 grams daily), is an effective agent in the prevention of tetany in parathyroidectomized animals. Magnesium tends to keep the calcium content of the blood serum above the tetany level. It is suggested that magnesium, by uniting with the excess phosphorus, keeps the calcium in solution. The sedative effect of magnesium greatly reduces the excitability of the central nervous system whereby the more violent symptoms of tetany are held in check. Magnesium-treated thyro-parathyroidectomized dogs, kept free from tetany for about forty days, become readjusted to the loss of the parathyroids and may permanently recover and be placed on a full meat diet without ill effects. The lactates of cadmium, sodium and potassium, tried in connection with the magnesium experiments, were found to be ineffective in preventing or relieving tetany.—R. G. H.

Growth of the thymus—its relation to status thymicolymphaticus and thymic symptoms. Boyd (E.), *Am. J. Dis. Child. (Chicago)*, 1927, **33**, 867-879.

Report of a study of 324 autopsies on all children in the author's institution between the ages of 2 weeks and 15 years who died in the last two years. The weight of the thymus was recorded in 45.5 per cent. The thymus in the newborn shows a temporary loss of weight which is probably concomitant with the normal loss in body weight. The fetal type of thymus is broad and the infantile type elongate. This change in form is produced during the first two weeks of life by the expansion of the lungs. Thymic symptoms may be produced during the first year of life by mechanical pressure of a normal gland on mediastinal structures, especially on the recurrent laryngeal nerve. The fluctuations in the weight of the thymus at any age period are concomitant with fluctuations in body weight. The growth curve of the thymus in a well nourished child is of the same type as that of the lymphoid tissue in general. The author's records do not show any case in which pressure on the trachea by the thymus caused death.—M. B. G.

The antagonistic functioning of thymus and thyroid. Investigations on the tadpole. (Zur Frage der Entwicklungsmechanisch-An-

tagonistischen Wirkung der thymus und der Thyreoiden. [Versuche an Kaulquappen.] Krizenencky (J.) & Podhradsky (J.), Arch. f. Entwicklungsmechn. d. Organ. (Leipz.), 1926, 108, 68-83; Abst., Child Development Absts., 1, 59.

Aqueous extracts of thymus gland even in the largest doses (50 cc. extract to 500 cc. water) had no influence on the developmental changes of the tadpole, and no effect on the acceleration of these changes which is produced by thyroid extract. On growth in length it was also without influence acting alone, but when growth was checked by the thyroid, thymus in high concentration (32-50 cc. in 500 cc. water) worked antagonistically to stimulate the inhibited growth. The authors are not sure, however, whether this antagonism was exerted through the life processes of the animal or by direct action of one substance on the other (in vivo or in vitro). The results in general do not support the older view that thymus extract inhibits metamorphosis and increases growth.

Hodgkin's disease, primary in the thymus gland. Report of a case in an infant. Wallstein (M.) & McLean (S.), Am. J. Dis. Child. (Chicago), 1926, 32, 889-900.

The authors report what they consider the youngest patient with this condition in the literature, a female infant 4½ months of age. The illness began with patechial hemorrhages in the skin. Six weeks later the blood picture was that of an anemia with a low hemoglobin, low red blood cell count, slight polymorphonuclear leucocytosis and diminution in the number of platelets (80,000). The clinical course showed a combination of skin hemorrhages, thymic tumor, rapid involvement of abdominal and thoracic lymph nodes without enlargement of any superficial nodes, fever and death in six weeks. The autopsy showed a thymic tumor weighing 58 grams, with a picture of infectious granuloma. The skin lesions were well developed and characteristic of the disease.—M. B. G.

An unusual case of thymic hypertrophy. Thorpe (E. S.), Arch. Pediat. (N. Y.), 1927, 44, 127.

Lymphoblastic leukemia associated with marked thymus enlargement in a boy 7 years of age.—M. B. G.

Relation of thyroid to calcium metabolism. Aub (J. C.), Tr. Ass. Am. Physicians (Phila.), 1927; Abst., J. Am. M. Ass., 89, 149.

The blood calcium and blood phosphorus are normal in thyroid disease, but the amounts excreted are far above normal. In the normal control, thyroid administration raises the blood calcium and calcium excretion. In myxedema, calcium metabolism is lowered, but with administration of thyroid the blood calcium and the calcium excretion are raised. In one patient, a woman who had had

tetany for seven years, there was a deficiency of calcium. Parathyroid administration increased the blood calcium and also increased the calcium excretion.

Studies on the thyroid apparatus. XXI. The rôle of the thyroid and parathyroid glands in the growth of the central nervous system. XXXII. The rôle of the thyroid apparatus in the solids—water differentiation of the central nervous system during growth. Hammett (F. S.), *J. Comp. Neurol. (Phila.)*, 1926, **41**, 171; *Abst., Arch. Neurol & Psychiat. (Chicago)*, **17**, 818-819.

Both of these papers involve data concerning the same group of animals. Further contributions to the extensive studies that Hammett has previously published on the thyroid apparatus in the rat are found here in the records of weight changes of the brain and spinal cord of groups of albino rats subsequent to removal of the thyroid and parathyroid at six different ages ranging from 23 to 100 days (between weaning and maturity). In general, the growth of the central nervous system is retarded after the removal of either gland at any age. This degree of retardation is less than that of the body as a whole. This is considered to be the result of the difference in chemical make-up and in degree of response to the general lowering of the metabolic level. The degree of retardation of the central nervous system tends to increase with increase in the age of the animal at the time of thyroid removal, while in parathyroidectomized animals the degree of retardation is remarkably constant, not increasing with age. This difference from removal of the thyroid is taken by Hammett as a specific relation between the parathyroid and central nervous system and is traced to a toxemia that follows removal of the parathyroid. At the age of puberty (65 days in the male and 75 in the female) a distinct and significant adjustment in the growth response of the central nervous system to both types of glandular deficiency takes place. There is less retardation of growth before puberty and more retardation after puberty. The brain is more subject to this gonadal influence than is the spinal cord, and the male shows a greater response (increased retardation of growth) at the onset of puberty than the female. It is suggested that there may be a definite interrelation between gonadal activity and brain growth, which is unmasked by removal of the thyroid and parathyroid at the critical point. The fact that up to the establishment of puberty growth of the cord is not any more resistant to thyroid deficiency than growth of the brain, leads the author to discard his earlier hypothesis dealing only with the 75-day age, that the greater resistance of growth of the cord to removal of the thyroid is the result of differences in phylogenetic development of the cord, brain and thyroid gland. This fact also necessitates a modification of the interpretation that he made in an earlier paper, based on differences in chemical composition. The

studies in the second paper (XXII), dealing with the central nervous systems in the same animals, are concerned with the amounts of weight changes in solids and water after the removal of the thyroid and parathyroid glands as compared with normals. Normally, the percentage of solids, which is always by percentage increment greater than water, increases with age, while the percentage of water decreases. As in all, growth percentage increment decreases with age. Thyroid and parathyroid deficiencies likewise cause a greater retardation of increment in water than in solids in the central nervous system. Only at puberty are sex disturbances of water-solid differentiation significant. Increased retardation is greater in the brain than in the spinal cord and greater in the brain of the male than in the female, which correlates again with the observations noted in the first paper (XXXI). The distortion is greater in thyroid than in the parathyroid deficiency and is attributed to a lesser degree of nutritional disturbance in the parathyroidless group. In the cord in which lipid (myelin) constituents are greater than in the brain and in which protein (cell substances) is greater in amount, the greater resistance to metabolic disturbances is taken as a basis of the difference in distortion, the lipid being more resistant to glandular deficiency.

Studies of the thyroid apparatus. XLVII. The cyclic character of the response to parathyroid deficiency. Hammett (F. S.), *Am. J. Physiol. (Balt.)*, 1927, **81**, 349-354.

Body growth and tooth calcification in the parathyroidectomized albino rat run a cyclical course of retardation and acceleration, or breakage and repair in which the changes in tooth condition follow those of the body growth rate. An interpretation is suggested of the sequence of events and other phenomena exhibited in conditions of parathyroid deficiency based on the idea that the parathyroid glands subserve two functions, that of participation in the regulation of the calcium balance, and that of the prevention of the accumulation of toxic tetany producing compounds within the organism. A possible seasonal difference in sensitivity to parathyroid deficiency is indicated.—Author's Abst.

Further attempts to experimentally increase the hormone output by the thyroid gland. Hektoen (L.), Carlson (A. J.) & Schulhof (R.), *Am. J. Physiol. (Balt.)*, 1927, **81**, 487.

In dogs under barbital anesthesia and with the cervical sympathetic nerves severed, there is considerable spontaneous variation in the concentration of thyroglobulin in the thyroid vein blood as determined by the precipitin method. These variations appear not only in different dogs, but in the blood from the two thyroid lobes of the same dog, and in the blood from the same lobe during the course of a single experiment. In experiments on nine dogs, the

sympathetic nerve stimulation, direct thyroid massage, and intravenous adrenalin and pilocarpine failed to increase the thyroglobulin in the thyroid vein blood above that of the variations in the controls. In one experiment, stimulation of the nerves to the thyroid was followed by an increase in the thyroglobulin concentration greater than in the controls. This may be due either to increased rate of thyroid secretion or to decreased blood flow through the gland.—Authors' Abst.

Myxedema and myxedema therapy. Noble (E.), Arch. Pediat. (N. Y.), 1927, 44, 94-99.

The author considers the administration of thyroxine to be the most desirable form of organotherapy in myxedema, but not always available, due to its difficult preparation. He advocates as next best thyreoidin, standardized according to a universal scale. His experience shows him that a simple relation can be established between the optimum amount of thyreoidin and the sitting height of the patient. For every centimeter of the sitting height squared, 10 mikrograms (0.01 mg.) of such a thyreoidinum siccum pro die has to be prescribed. A table is appended for some sitting heights.—M. B. G.

Sensitiveness of suprarenalectomized rats to morphine. (Sensibilité à la morphine des rats surrenalectomisés.) Lewis (J. T.) & Torino (A.), Compt. rend. Soc. de biol. (Par.), 1927, 96, 217-219.

Bilateral adrenal ablation was performed on 273 rats. Since 55 per cent of these animals survived the results are in accord with the work of Rogoff and Necker. The toxic dose of morphine for the normal rat was found to be 0.4 mgm. per gm. When 0.04 mgm. per gm. was injected subcutaneously into a series of 52 rats which had been operated upon 2 weeks previously, 69.2 per cent died. With 30 rats which had survived 5 weeks, only 10 per cent died when the same dosage was injected. Using a dosage of 0.08 mgm. per gm., 67 per cent died, and with 0.1 mgm. per gm., 53.4 per cent died. When the dosage was increased to 0.20 mgm. per gm., 81.3 per cent did not survive. The complete extirpation of the glands was verified at autopsy. From their results the authors conclude that the adrenalectomized rat is more sensitive to morphine than is the normal rat.—E. Larson.

Reaction of chronic nephrosis to thyroid and parathyroid medication. Meakins (J. C.), Tr. Ass. Am. Physicians (Phila.), 1927; Abst. J. Am. M. Ass., 89, 149.

Improvement was noted in nephrosis as a response to thyroid and parathyroid medication. The effect was due to the readjustment of the calcium metabolism. A woman with recurrent attacks of edema, which was resistant to diuretics, was put on parathyroid medication

with good results. The urine contained casts and red cells. The urea was normal. The blood calcium was low. On parathyroid extract, 50 units a day, there was a prompt increase in serum calcium, marked increase in urine output and drop in weight. When the parathyroid was stopped, the edema returned. In case of edema and ascites, and a reverse of the albumin globulin ratio, there was an increase in blood cholesterin, the blood calcium being low. There was no response until the eighth day, when the patient responded to thyroid. This was a case of mixed glomerular nephritis with nephrosis. In another case, in which there was edema, the parathyroid had no effect on the weight. With high protein diet there was response in weight, but none in the plasma protein. A drop in weight followed thyroid medication. The cholesterin in the blood dropped. There was evidently an endocrine imbalance in these cases which varied in different patients; sometimes thyroid was effective, sometimes parathyroid. Sometimes it was not due to calcium disturbance. The plasma proteins may not be changed.

Clinical investigation into the basal metabolism in diseases of the thyroid gland. Moller (E.), *Acta Medica Scandinavica* (Supplementum XXI), (Copenhagen), 1927, 1-219.

It is the general opinion that Graves' disease is always accompanied by a rise in the basal metabolism. On perusing the literature it was found that proof is never furnished of the truth of this view. A record of 89 cases of Graves' disease and Graves' disease forme fruste is furnished. Only cases which exhibited goitre, tremor and permanent tachycardia were regarded as true Graves' disease. To this group belong 70 of the 89 patients; the other 19 were classed as Graves' disease forme fruste. In these 89 patients, 721 determinations of the basal metabolism were made. An investigation was made as to whether the results showed any causal connection with the sex and age of the patients or the duration of the disease. The basal metabolism was found to vary from 99.1 per cent to 190.2 per cent in Graves' disease; in 10 per cent of the patients it was below 110 per cent. In the formes frustes it was found to vary from 95.8 per cent to 138.1 per cent; in 69 per cent of the patients it was below 110 per cent. Examinations of the stomach secretion were made in 40 patients with Graves' disease; 17 had achylia. Relatively many of these 17 had suffered from diarrhoea. Arythmia cordis was present in 5 cases. The conclusion is reached that the demonstration of a basal metabolism lying within the normal limits should not exclude the diagnosis of Graves' disease. The order of frequency of the commonest symptoms is: tachycardia, tremor, goitre, nervousness, increase in the basal metabolism, palpitation, increased sweat secretion and exophthalmos. In 3 cases death ensued in connection with acute psychosis. These cases had not previously shown a specially high basal metabolism. During treatment with

rest and overfeeding a fall in the basal metabolism of 10-20 per cent occurred in most cases in the course of 2-4 weeks. The effect of x-ray treatment was investigated in 33 cases. On the whole the basal metabolism fell at the same time as the other symptoms declined, but usually this decrease did not begin until the improvement had asserted itself in another way, just as the basal metabolism increase in several cases was one of the symptoms to disappear last. As a rule, the subjective symptoms diminished first. It is regarded as most probable that in at least half of the cases x-ray treatment caused a marked improvement and not infrequently a cure. The standpoint is adopted that subjects which do not respond well to medical and x-ray treatment should, as a rule, be operated upon without delay. Basal metabolism values ranging from 113.7 to 129.2 per cent were found in 33 determinations in 5 patients with toxic adenoma of the thyroid gland. Three cases of adenoma without hyperthyroidism showed normal values. Of 21 patients with simple goitre, 20 had a basal metabolism within the normal limits, but in one it was 79.7 per cent. In 18 patients with myxoedema, 2 with cachexia strumipriva and 3 with slight hypothyroidism, 180 determinations were made. In all the untreated cases of myxoedema and cachexia strumipriva there was a low value. The values seemed not to go below about 60 per cent, which value was, therefore, assumed to correspond to the total deficit in the functional activity of the thyroid gland. The 3 cases of slight hypothyroidism showed values around 90 per cent. Nineteen of these patients upon thyroid treatment showed a rise in basal metabolism. The rise did not begin until after 2-3 days, and did not reach its maximum for 2-8 weeks. The rise in the basal metabolism was an early sign of improvement, while the subjective symptoms often disappeared last.—R. G. H.

The first occurrence of secretory products and of a specific structural differentiation in the thyroid and anterior pituitary during the development of the pig foetus. Rumph (P.) & Smith (P. E.), *Anat. Record.* (Phila.), 1926, **33**, 289-298.

The intraperitoneal injection of extracts from the thyroid of the 7 cm. (crown-rump length) pig foetus affords no stimulus to metamorphosis in the hypophysectomized tadpole. The injection of the thyroid of the 9 cm. pig foetus gives the response characteristic of injections of the thyroid of the adult. Follicle and colloid formation is evident in the thyroid of the 9 cm. pig foetus, but is absent in the thyroid of the 7 cm. foetus. No response to the intraperitoneal injection of anterior hypophyseal substance from the 14 cm. or 16 cm. pig foetus was given by the hypophysectomized tadpole. A slight response was elicited by the anterior pituitaries of the 26 cm. to 28 cm. pig foetus. The cells characteristic of the adult anterior pituitary are not present in the 14 cm. foetus, and but few are present in the 16 cm. stage. They are numerous in the 26 cm. to 28 cm. foetus.—Authors' Summary.

Endocrinology

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**CARBOHYDRATE METABOLISM IN
HYPERTHYROIDISM***

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I have attempted in this study to investigate the blood sugar and glycosuria in cases of hyperthyroidism. When this investigation was started it was my intention to study the blood sugar and glycosuria in every type of disease of the thyroid gland, so that this series includes about ten cases of colloid goiter without hyperthyroidism. The cases which were studied were not consecutive but were chosen because they showed either glycosuria or hyperglycemia two and one-half or more hours after a meal.

The carbohydrate metabolism has been determined in each case by glucose tolerance tests made uniformly by the following method: One hundred grams of glucose in 250 cc. of ice-cold water plus the juice of one lemon is given by mouth in the morning before any food is taken. Blood is taken for sugar estimations before the glucose is administered and at successive intervals of one-half, one, two, three and four hours thereafter.

*Presented in abbreviated form at the Eleventh Annual Meeting of the Association for the Study of Internal Secretions, Washington, D. C., May 17, 1927.

TABLE I
DATA IN 92 CASES OF HYPERTHYROIDISM AND SIMPLE GOITER IN WHICH GLUCOSE TOLERANCE TESTS WERE MADE

Number	Date When Seen	Glycosuria First Discovered	Fasting Blood Sugar	Sex	Age	Weight			Thyroidectomy	Remarks
						Weight	% Overweight	% Underweight		
100731	3-15-21	Negative	165	F	55	210	65	...	5-22-20	Note decreased tolerance when hyperthyroidism developed.
102977	8-24-21	1-9-22	256	F	40	9-28-20	
105096	8-2-21	8-3-21	112	M	64	12-1-26	
109856	1-24-22	1920	87	M	34	190	28	
111876	4-7-22	1920	129	M	55	Thyroidectomy 1911. Gained 50 lbs., 3 mos. Normal B. S. 1 year later.
116219	9-1-22	9-1-22	85	M	43	
120165	1-16-23	9-10-22	187	F	52	140	10	...	8-15-23	
122866	4-17-23	4-17-23	141 (3)	F	50	30	...	
123327	6-2-23	4-30-26	77	F	49	215	53	4-15-26 glycos. after influenza.
127104	9-18-23	9-2-23	76	F	49	5-4-23	
131355	12-14-23	3-1-23	110	M	38	140	12-18-23	
133039	2-8-24	2-9-24	76	M	39	145	6	...	3-13-24	
134132	3-10-24	Negative	145	M	72	175	30	Lost 40 lbs. in 6 mos. Quite emaciated. Lost 15 lbs. Lost 50 lbs. Lost 45 lbs.
145891	1-12-25	1-12-25	216	F	40	
147421	2-17-25	Negative	280	F	60	92	...	41	...	
149341	4-2-25	1-2-25	275 (3)	F	52	8-18-25	
152201	6-9-25	1923	95	F	20	9-3-25	Lost 40 lbs. in 6 mos. Quite emaciated. Lost 15 lbs. Lost 50 lbs. Lost 45 lbs.
152737	8-20-25	Negative	141 (2)	F	32	10-15-25	
155420	8-20-25	7-1-25	98	F	57	131	9-21-26	
155744	10-6-25	Negative	114	M	30	111	10-28-25	
157541	10-17-25	10-6-25	114	F	45	26	...	Lost 40 lbs. in 6 mos. Quite emaciated. Lost 15 lbs. Lost 50 lbs. Lost 45 lbs.
158002	10-23-25	7-7-25	136	M	43	140	4-2-26	
158016	11-5-25	Negative	55	F	54	12-14-25	
158782	11-11-25	11-11-25	95	F	47	12-22-25	
149049	12-2-25	11-11-25	98	M	50	1-19-26	Lost 40 lbs. in 6 mos. Quite emaciated. Lost 15 lbs. Lost 50 lbs. Lost 45 lbs.
150737	12-10-25	Negative	226 (4)	F	42	12-8-26	
160681	12-10-25	1923	219	F	46	
160731	12-15-25	1924	94 (3 3/4)	F	40	154	
162170	12-20-25	2-4-26	186	F	32	Lost 40 lbs. in 6 mos. Quite emaciated. Lost 15 lbs. Lost 50 lbs. Lost 45 lbs.
164227	3-23-26	Negative	101 (1)	M	26	220	...	59	...	

TABLE I—Continued

Number	Date When Seen	Glycosuria First Discovered	Fasting Blood Sugar	Sex	Age	Weight			Thyroidectomy	Remarks
						Weight	% Over-weight	% Under-weight		
165508	4-19-26	4-19-26	179 (3¼)	M	29	128	29	...	5-8-26	Lipodystrophy and hyperthyroidism. Thyroidectomy 1919. Acromegaly. Thyroidectomy in 1916. Lost 33 lbs.
165767	4-26-26	Negative	101 (4½)	F	20	174	4-28-26	
165752	4-26-26	Negative	102	F	34	160	55	
167566	6-1-26	Negative	97 (4)	F	48	296	...	33	11-9-26	
167620	6-2-26	6-2-26	134 (2)	F	58	115	...	21	11-10-26	Thirst, frequency, nervousness. Thyroidectomy 1917. Lost 50 lbs. in 6 mos.
167654	6-2-26	6-23-26	85	F	49	95	25	
168150	6-12-26	Negative	89 (2½)	F	27	112	...	10	2-14-27	
168510	6-18-26	Negative	111	F	10	55	7-16-26	
169053	6-29-26	Negative	66	M	29	140	...	2	...	Lost 17 lbs. Lost 35 lbs. Marked nocturia. Loss of weight.
169513	6-29-26	Negative	68	F	17	104	...	25	8-24-26	
170000	7-19-26	1-?-26	93 (3)	M	54	147	9-3-26	
170804	8-6-26	Negative	96	F	30	20	...	
171841	8-27-26	1-24-27	192	F	45	98	...	10	9-16-26	Hyperthyroidism developed after use of iodized salt.
171949	8-30-26	Negative	105 (6)	F	33	113	...	17	...	
172110	9-1-26	Coma 5-25	187 (4)	M	36	135	...	61	...	
172319	9-3-26	9-3-26	76	M	51	102	
172346	9-7-26	9-7-25	102F	M	56	178	...	21	12-1-26	Hyperthyroidism developed after use of iodized salt.
172311	9-7-26	9-7-26	72	M	35	140	8-20-26	
172566	9-10-26	Negative	122	M	50	115	...	27	9-25-26	
172569	9-10-26	9-10-26	88	F	51	118	...	11	9-28-26	
172758	9-14-26	Negative	146 (2½)	F	48	167	...	9	...	Hyperthyroidism developed after use of iodized salt.
173493	9-29-26	9-28-26	270 (2)	F	55	130	...	25	11-4-26	
173894	10-7-26	10-25-26	92 (5½)	F	51	99	...	47	11-4-26	
174309	10-18-26	7-18-26	173 (1½)	F	56	81	...	18	...	
174593	10-22-26	Negative	150 (3¼)	F	61	110	Hyperthyroidism developed after use of iodized salt.
175328	11-8-26	Negative	139 (4)	M	60	111	...	29	3-17-27	
175632	11-15-26	Negative	73	M	25	151	...	34	11-30-26	
175685	11-15-26	10-13-26	97	M	62	160	11-30-26	
175766	11-17-26	11-17-26	194 (3½)	F	56	122	3-14-27	
175849	11-18-26	11-18-26	119	F	49	140	12-18-26	Hyperthyroidism developed after use of iodized salt.
176197	11-29-26	Negative	125 (3½)	F	37	151	

TABLE I—Concluded

Number	Date When Seen	Glycosuria First Discovered	Fasting Blood Sugar	Sex	Age	Weight			Thyroidectomy	Remark
						Weight	% Over-weight	% Under-weight		
176410	12-1-26	12-8-26	169	F	59	132		10	12-16-26	
176905	12-15-26	Negative	113	F	30	89		51	1-5-27	
178015	1-15-27	Negative	99	F	19	105		10	2-2-27	
178032	1-17-27	Negative	125	F	35	112		10		
178213	1-20-27	Negative	152	F	69	176	30		1-28-27	
178231	1-20-27	1-20-27	81	F	34	145		5	1-21-27	
178470	1-27-27	2-9-27	155	F	46	116		10	2-8-27	
178688	2-1-27	2-2-27	400	F	45	150	5		12-1-22	
178736	2-2-27	2-2-27	130	F	48	95		26	2-18-27	
178992	2-8-27	2-8-27	161	F	39	153	16			
179177	2-12-27	Negative	110	M	13	101	5			
179222	2-14-27	2-14-27	167	F	59	167	34			
179214	2-14-27	2-14-27	116	F	39	116		22	2-24-27	
179260	2-15-27	Negative	163	F	53	137	10			
179357	2-16-27	2-16-27	272	F	56	94		20		
179934	3-2-27	3-2-27	255	F	58	124		30	3-21-27	
179977	3-3-27	1917	179	M	59	185	37		3-22-27	
180132	3-7-27	Negative	97	F	23			10	3-21-27	
180192	3-10-27	3-22-27	98	F	31	53		10	3-22-27	
180206	3-11-27	Negative	97	F	10			10	3-21-27	
180388	3-13-27	3-14-27	134	F	40			10	3-25-27	
180565	3-17-27	Negative	133	F	43	123		10		
180592	3-18-27	Negative	140	F	26	117		12		
180714	3-21-27	Negative	161	F	51	97		34		
180739	3-22-27	Negative	178	F	46	117			4-4-27	
180770	3-22-27	Negative	114	M	29	153				
180780	3-22-27	Negative	98	M	48	330	82		3-30-27	
181458	4-6-27	Negative	97	M	25	132		16		
181530	4-7-27	4-7-27	147	M	48	84		45		
181509	4-7-27	Negative	117	F	51	86		42	4-15-27	

Two hundred cubic centimeters of ice-cold water is given hourly by mouth. Urine is taken at the same intervals—with the exception of one-half hour after the ingestion of the glucose—for both qualitative and quantitative examinations for sugar. This routine has been identical for all patients in this group with the exception of two children 10 and 12 years of age, respectively, who received 75 gm. of glucose. The blood sugar estimations have been made by the Myer-Benedict method, the blood being oxalated, and tested immediately in most cases, although in a few instances it was kept on ice for two hours before it was tested. Basal metabolism estimations have been made whenever this was feasible.

TABLE II

SEX AND AGE INCIDENCE IN CASES OF HYPERTHYROIDISM IN WHICH GLUCOSE TOLERANCE TESTS WERE MADE

Decades.....	1	2	3	4	5	6	7	8	Total No. Tests
Male.....	..	1	8	9	6	7	2	..	33
Female.....	2	4	7	14	16	20	3	1	67

TABLE III

PERCENTAGE OF OVERWEIGHT AND UNDERWEIGHT IN CASES OF HYPERTHYROIDISM IN WHICH GLUCOSE TOLERANCE TESTS WERE MADE

Percent.....	5	10	15	20	25	30	35	40	45	50	55	60	65	85	Total
Over weight..	3	2	..	1	1	5	1	1	2	1	1	1	19
Under weight	2	9	2	5	5	6	3	..	3	1	1	..	1	..	38

TABLE IV

THE AMOUNT OF SUGAR EXCRETED DURING GLUCOSE TOLERANCE TESTS

Sugar, gram.....	1	2	3	4	5	5-10	10-20	20-30	30-40	40-50
Number of cases.....	24	17	5	4	6	13	7	1	2	2

In Tables I-IV are given the pertinent data in the 92 cases in the series here presented. One hundred glucose tolerance tests have been made in this series, as in several cases the test was repeated. The ages range from 10 years to 72 years. Either glycosuria or hyperglycemia was present in most of these

cases, this finding leading to the glucose tolerance test in order to determine the degree of the carbohydrate derangement. In such a study as this a large number of basic observations must be made if one is to secure sufficient follow-up data from which to draw conclusions. As these patients come from all over the United States, in only a small group can it be hoped that sufficient data will be secured for a further study.

Nineteen of the patients were overweight and 38 were underweight. The tendency in cases of hyperthyroidism is to lose weight, this being probably due to the increased metabolism which makes a patient burn up, first, his superfluous fat and, later, his body protein. Some of these patients were markedly emaciated. Those in whom the carbohydrate metabolism is considerably disturbed lose weight because of the imperfect oxidation of the carbohydrate and the consequent loss of sugar through the urine.

Two patients in this series died—a mortality rate of 2.1 per cent. In one of these cases death was due to a postoperative pulmonary collapse; the other case was that of an old woman 72 years of age with very severe hyperthyroidism, who died from collapse the day after operation.

In this series of 92 cases thyroidectomy was performed in 57, or 62 per cent. In a few of these cases—perhaps ten—only ligations have thus far been performed, and the thyroidectomy will be done at a later date. In one case which will be reported in another section of this paper, the symptoms of hyperthyroidism disappeared entirely as the result of insulin treatment alone. In another case, not included in this series, a patient with very severe hyperthyroidism associated with severe diabetes has not responded in the least to large doses of insulin, as far as the symptoms of hyperthyroidism are concerned, though the diabetes is controlled. This patient has been under observation since October, 1925, and there are so many interesting phases about his case that it will be reported later, when the problems which it presents are more nearly solved.

A study of the tolerance tests shows a range of response from the perfectly normal to that which indicates the presence of very severe diabetes. There is no definite line of demarcation between the normal and the diabetic state, and no matter

where one might put the dividing line, the high incidence of diabetes would still be evident.

In this study I have tried to call attention to the fact that there is a disturbance of carbohydrate metabolism in hyperthyroidism, and that this is not a rare finding is evident. I feel that such a disturbance is the result of the great drain on the insulogenic mechanism due to the increased metabolism. Such an increased drain is of no consequence in individuals who have a good reserve in the islands of Langerhans, but it is of great consequence in cases in which this insulogenic reserve is small. These cases, and these cases only, I think, show hyperglycemia. They may show glycosuria or they may not, since this depends on the height of the renal threshold in the individual case as well as upon the corresponding degree of hyperglycemia.

The permeability of the renal filter seems to be increased in some cases. Whether it is increased in all cases I cannot say, since, to determine this, would necessitate definite studies of the condition of these individuals before hyperthyroidism developed in order to compare the renal threshold at that time

TABLE V
PRESENCE AND ABSENCE OF GLYCOSURIA DURING GLUCOSE
TOLERANCE TESTS

	Before Ingestion of Glucose	After Ingestion of Glucose			
		1 Hour	2 Hours	3 Hours	4 Hours
Glycosuria present....	19	75	81	58	38
Glycosuria absent.....	81	25	19	42	62

Glycosuria present at some time during glucose tolerance test in 81 cases.
Glycosuria absent during the entire glucose tolerance test in 19 cases.

with the threshold during the active stage of hyperthyroidism. We know that both in animals and in man thyroidectomy eliminates glycosuria; but it also reduces glycemia, hence this fact proves nothing as far as the renal threshold is concerned.

The glucose tolerance estimations in this series showed fasting glycosuria to be present in 19 tests and absent in 81 tests (see Table V). Glycosuria was present in the majority of cases in the first, second and third hours, and was absent in the ma-

jority of cases in the fourth hour. It was present at some time or other during the test in 81 cases and absent during the entire test in 19. Sixty-six per cent of these cases present an impaired tolerance; only 34 per cent showing a normal curve. This general impairment of glucose tolerance can best be demonstrated by the 100 curves which are given in Figures I to VII.

The amount of sugar excreted varied from one to 50 grams. In most cases (69 per cent) less than 5 grams was excreted; in 85 per cent less than 10 grams was excreted; and in only 15 per cent was more than 10 grams of sugar excreted.

It is obvious that glycosuria in itself alone does not tell us a great deal regarding the status of the carbohydrate metabolism, unless it is marked and unless we know also the blood sugar response to the ingestion of carbohydrate and the level of renal permeability to sugar. The excretion of sugar by a patient with a low threshold is usually of little or no significance.

According to our observations in this series the state of hyperglycemia is not proportional to the severity of the hyperthyroidism. Were hyperglycemia directly due to hyperthyroidism then certainly the degree of hyperglycemia would bear a direct relation to the degree of hyperthyroidism—but this is not the case. In some of the cases which showed the highest hyperglycemia the degree of hyperthyroidism was the mildest. If in some cases mild hyperthyroidism is sufficient to bring about a diabetic state, and in others severe hyperthyroidism leaves the carbohydrate tolerance undisturbed, one naturally asks, "Why?" It seems to me that the evidence points to but one explanation, namely, that in the former group in which diabetes is produced the islands of Langerhans have a small reserve and thus easily become exhausted, hence a diabetic state is easily brought about by any condition which brings a further strain, in this instance the hyperthyroidism being the disturbing influence.

Figures I, II, III, IV, V, VI, VII, following. Charts showing findings in a series of 100 glucose tolerance tests made in cases of hyperthyroidism and simple goiter.

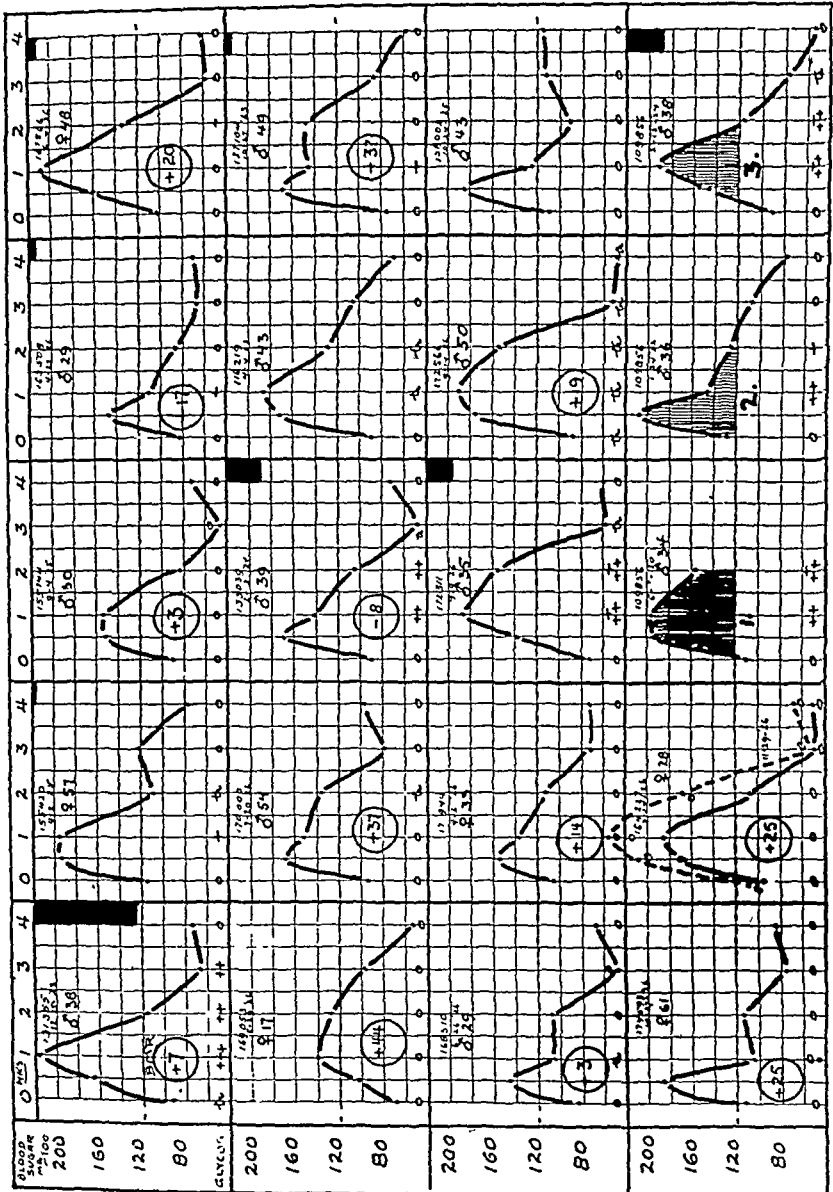


Figure I

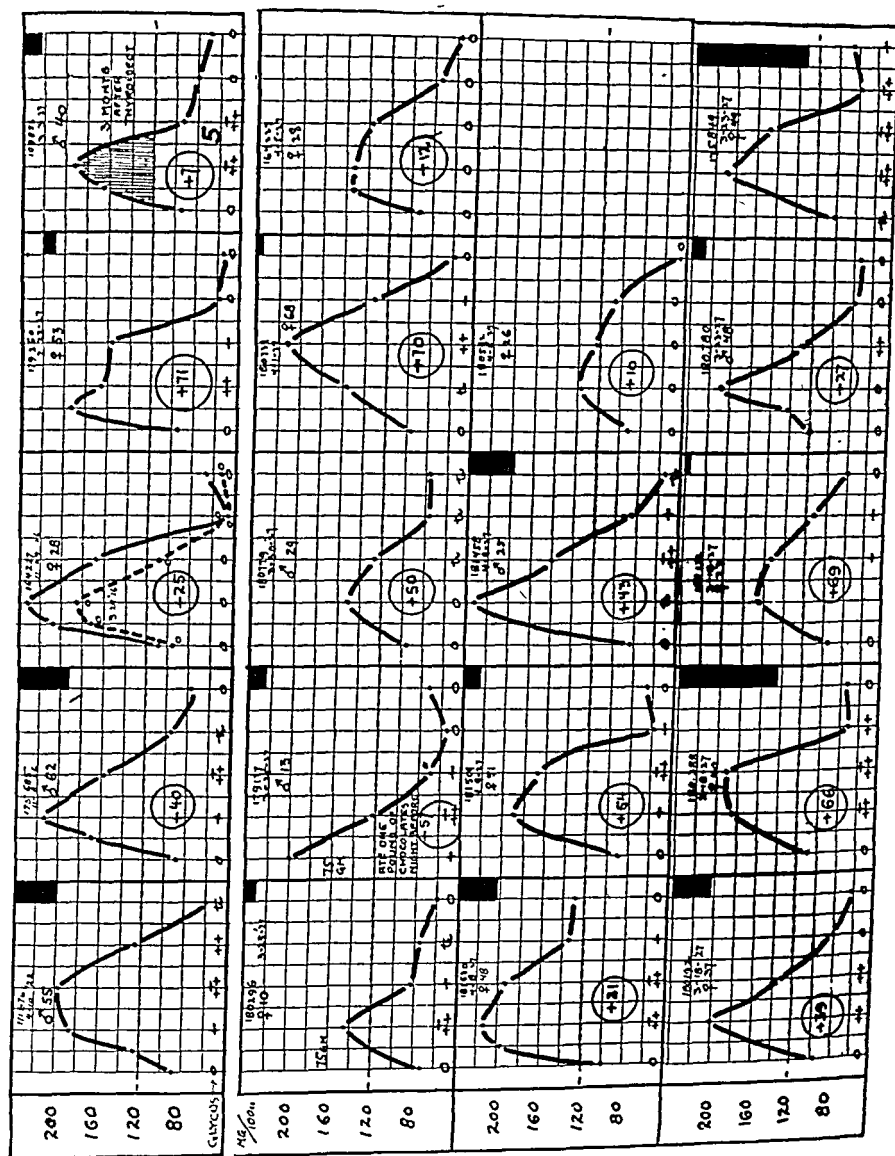


Figure II

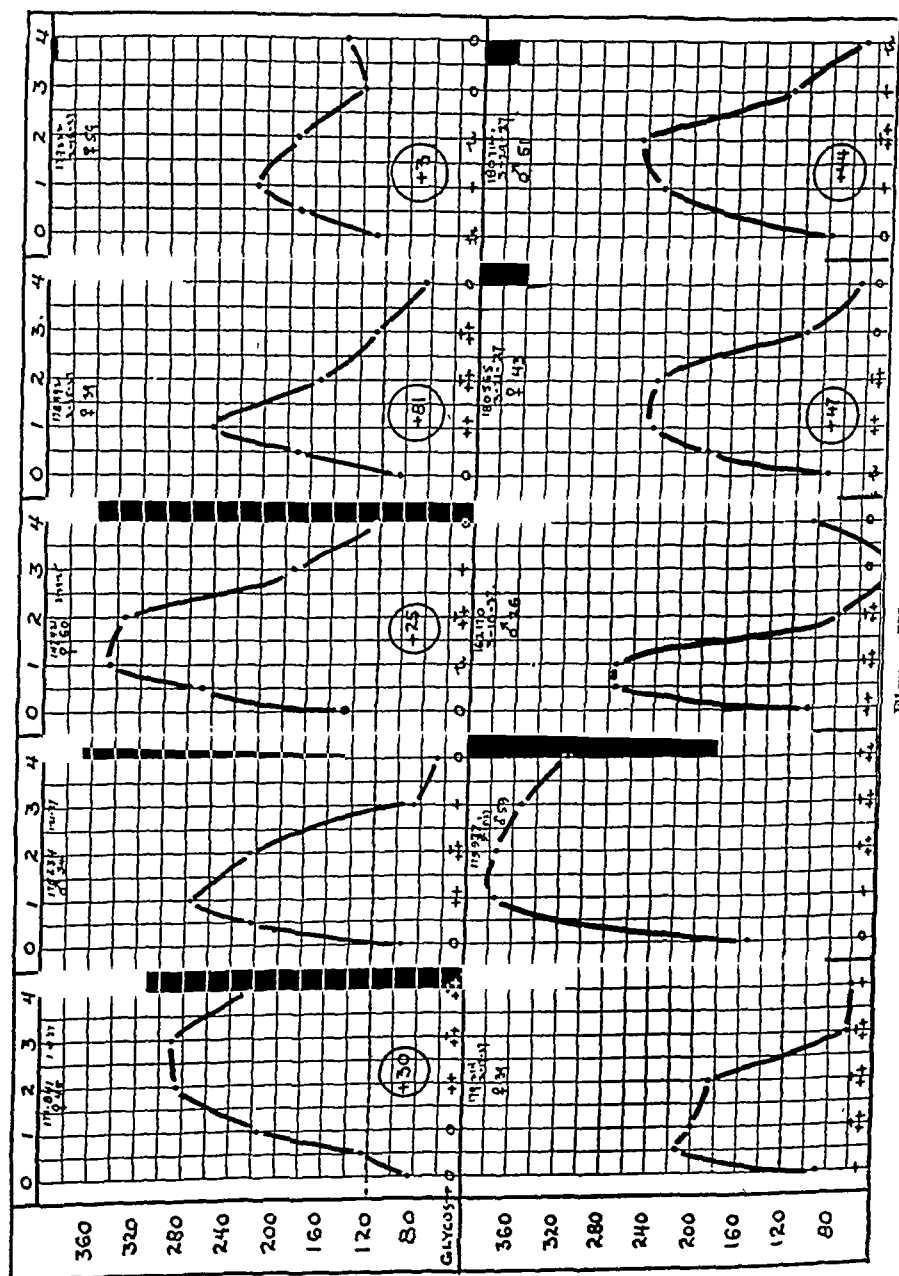


Figure IV

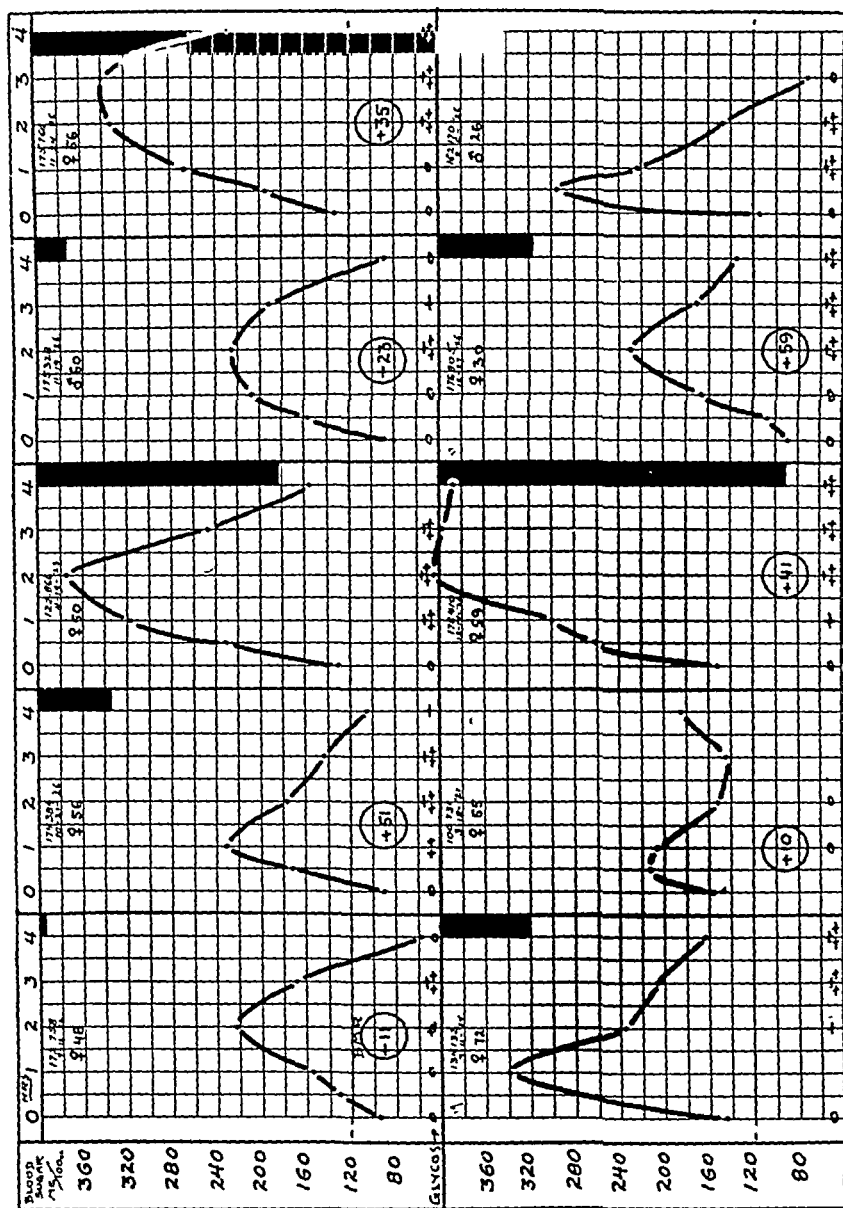


Figure V

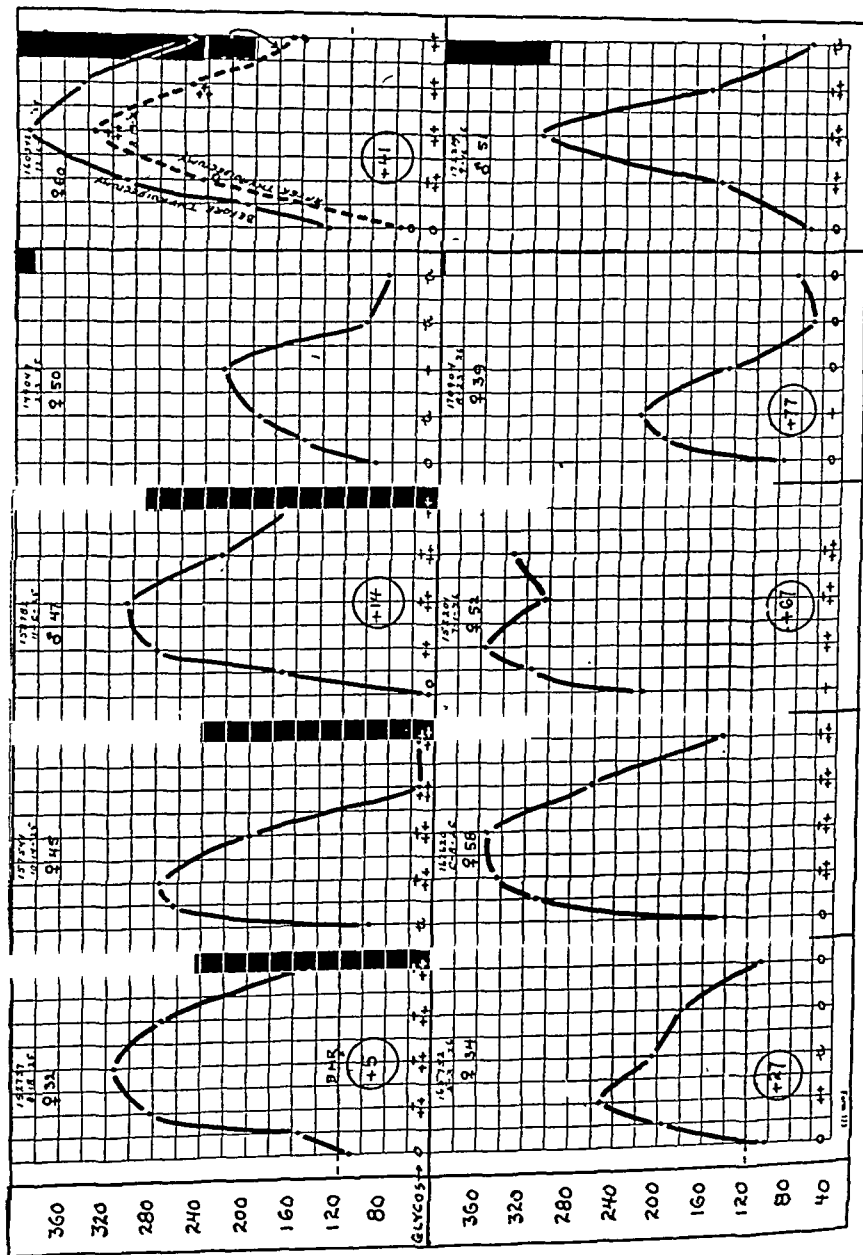


Figure VI

The relationship of the basal metabolic rate to the glucose tolerance in this series is shown in Table VI. It will be noted that in 40 of these cases the curve was diabetic or prediabetic in type and the basal metabolic rates ranged from minus three to plus 90 per cent. The case in which the metabolism was minus three, however, was one of simple goiter, not hyperthyroidism. In the 34 cases in which the glucose tolerance curve was normal in type, the basal metabolic rate varied from minus three per cent to plus 80 per cent.

TABLE VI

THE RELATIONSHIP OF BASAL METABOLIC RATE TO GLUCOSE TOLERANCE
IN 66 CASES

	Minus	Plus 1-10	Plus 10-20	Plus 20-30	Plus 30-40	Plus 40-50	Plus 50-60	Plus 60-70	Plus 70-80	Plus 80-90	Total
Number cases...	3	11	8	11	10	10	4	4	4	1	66
Diabetic or pre-diabetic curve...	2	5	3	7	5	8	3	4	2	1	40 (60.6%)
Normal glucose tolerance curve.	1	6	5	4	5	2	1	0	2	0	26 (39.4%)

On the basis of this study it seems evident that the mild derangements of the carbohydrate tolerance that have been observed in this series of cases are but functional disturbances, which disappear when the offending factor, the thyroid, is eliminated either by operation or by other treatment. As for the effect of insulin on hyperthyroidism, one may reason that it perhaps improves the patient's general metabolic condition, giving him a better chance to store glycogen in the liver and thus to combat acidosis; to store glycogen in the heart muscle and thus to give it a better chance to do its work; and to store glycogen in the muscles and thus to eliminate the instability of the organism in general. There is perhaps nothing specific about its action.

The medical problem involved in these cases is to protect these individuals with a decreased carbohydrate tolerance, rather than to let them drift along unprotected toward diabetes. They should be under surveillance until the physician has satisfied himself that stability has been established. In most of these cases the glycosuria disappears after thyroidectomy and the carbohydrate tolerance is restored to normal; in a few cases

this does not happen. It is important, therefore, to make post-operative examinations to determine whether or not the carbohydrate metabolism has been restored to normal; and when this has not happened, to institute such measures as are indicated. It is much easier to keep a mild diabetic in the mild stage than to treat him successfully after a severe stage has developed.

METHOD FOR THE DETERMINATION OF THE RENAL THRESHOLD.

Since the determination of the renal threshold is essential for the correct interpretation of glycosuria, it seems well to describe in some detail our method for its estimation. This can best be done by citing two concrete examples. In Figure VIII are shown the glucose tolerance curves of two cases in this series. The blood sugar curve is represented by the heavy black line, which is intersected by dots that indicate actual blood sugar estimations. At the bottom of each chart the presence of sugar in the urine is indicated by the plus sign, its absence by zero.

An examination of the upper chart in Figure VIII will show that there was no fasting glycosuria when the fasting blood sugar was 130 mgm. per 100 cc. At the end of one hour the urine sugar was three plus and the blood sugar 319 mgm. per 100 cc. It is evident that the renal threshold lies somewhere between these two points; and an approximate figure can be obtained by taking the average of the two blood sugar values, viz., 224. The blood sugar level at the end of the second hour was 375, and at the end of the third hour it was 246 mgm. per 100 cc., and glycosuria was present at the time of each of these estimations. But note that at the end of the fourth hour no glycosuria was present and that the blood sugar had fallen from 246 to 155 mgm. per 100 cc. at the end of the third hour. This must mean that no sugar was excreted while the level was falling from 375 to 246 mgm. per 100 cc., as otherwise some sugar would appear at the end of the fourth hour. The excretion of sugar therefore must have stopped at somewhere about 246 mgm. per 100 cc., which indicates that the original average figure of 224 mgm. per 100 cc. was too low, and that the renal threshold was at or above 246 mgm. per 100 cc.

In the lower curve in Figure VIII it is shown that in this case there was a trace of sugar in the urine when the fasting

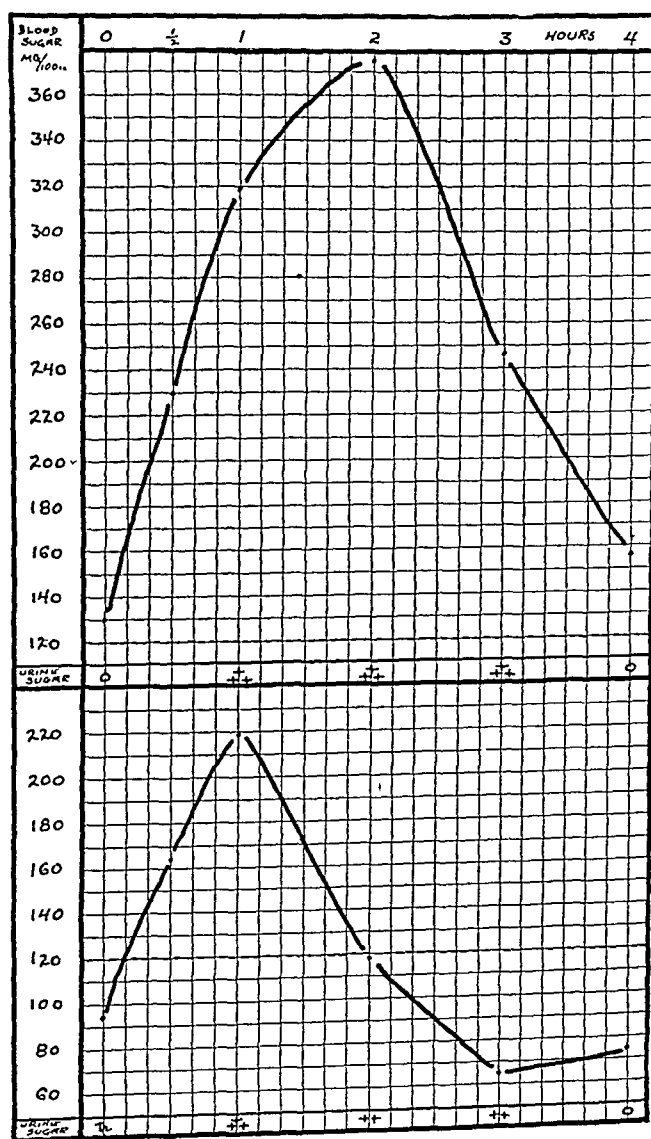


Figure VIII. Charts showing findings in two glucose tolerance tests illustrating the method of estimating the renal threshold (see text).

blood sugar was only 94 mgm. per 100 cc. Does this mean that the threshold lies at or below this blood sugar level? Not at all, because we do not know what was the blood sugar level at the time of the preceding voiding of urine. It is necessary therefore to discard this fasting glycosuria finding and to get what information we may from the following estimates. Between the second and third hours the blood sugar dropped from

118 to 64 mgm. per 100 cc. and there was glycosuria when the latter estimation was made. But although the blood sugar rose between the third and fourth hours from 64 to 74 mgm. per 100 cc., there was no glycosuria at the end of the fourth hour. It is obvious, then, that the glycosuria at the end of the third hour was due to sugar excreted at 118 or below. An average of the third and fifth estimations, therefore, must give us the approximate level of the renal threshold in this case, viz., 96 mgm. per 100 cc.

While this method does not give us absolutely accurate figures, nevertheless it is evident that the findings thereby secured are far more reliable than those obtained by our former procedure of taking the lowest figure at which glycosuria appeared and totally disregarding the preceding blood sugar value.

When glycosuria is present throughout the test no threshold value can be stated; and the same is true when no glycosuria is present at any time during the test.

Table VII shows the findings in 73 glucose tolerance curves in which the level of the renal threshold has been calculated in this manner. It is striking that the threshold was below 120

TABLE VII

RENAL THRESHOLD IN 73 GLUCOSE TOLERANCE TESTS MADE IN CASES OF HYPERTHYROIDISM AND SIMPLE GOITER

Blood sugar mg./100 cc.	60-70	71-80	81-90	91-100	101-110	111-120	121-130	131-140
Number of cases.	3	3	0	6	3	11	7	4
Blood sugar mg./100 cc.	141-150	151-160	161-170	171-180	181-190	191-200	201-210	211-220
Number of cases.	4	7	5	4	1	1	3	2
Blood sugar mg./100 cc.	221-230	231-240	241-250	251-260	261-270	271-280	281-290	291
Number of cases.	4	1	1	1	1	0	0	1

mgm. per 100 cc. in 26 cases, or 35.6 per cent, and that in three cases it was below 70 mgm. per 100 cc. These values on the whole seem lower than would be true of a like series of average clinical cases. Whether the renal permeability is greater in hyperthyroidism I am not prepared to state; I can only offer my findings. Figure IX suggests that this may be a justifiable assumption, as more sugar—5.46 grams—was excreted before operation, when the basal metabolic rate was plus 81 per cent,

than was the case two months after thyroidectomy, when the second tolerance test was made, and only 0.15 gram was excreted; though as the second curve was as high as the first and was more prolonged, one would expect that at least as much if not more sugar would have been excreted. Our findings certainly suggest that there is an increased permeability of the renal filter during active hyperthyroidism.

CRITICAL REVIEW OF THE LITERATURE

I have endeavored to review all the recent reports in the French, German, Czech, English and American literature. At the risk of some repetition this extensive material is critically discussed under the headings which appear pertinent to this general study of the relation of hyperthyroidism to carbohydrate metabolism.

Pathological Changes in the Pancreas Associated with Hyperthyroidism. In 1921 Holst (1) made postmortem studies in four cases in which glycosuria had been associated with exophthalmic goiter. A decrease in the number of the islands of Langerhans and other histological changes in the pancreas were found. There is reason to believe that in Graves's disease the well known anomalies in sugar metabolism are induced by gross anatomical changes of the pancreas in some cases, whereas slight anomalies in the sugar metabolism are only functional in character. In Holst's series seven patients suffering from Graves's disease with alimentary glycosuria were all cured by hemistru-mectomy. In three patients with glycosuria the glycosuria disappeared after the operation; in another case diabetes developed and the patient died, although she had previously undergone an operation for exophthalmic goiter. Thyroidectomy, therefore, appears to give good results in mild cases of glycosuria and poor results in severe cases. The glycosuria in experimental diabetes produced by partial extirpation of the pancreas disappears or decreases after thyroidectomy. Normally the thyroid appears to exert an inhibitory action over the pancreas—a point which Allen (2) questions but in support of which Rohdenburg (3) offers an explanation based on pathological evidence. These facts seem to favor the hypothesis that even in the usual cases of non-thyrogenous diabetes there is a therapeutic possibility

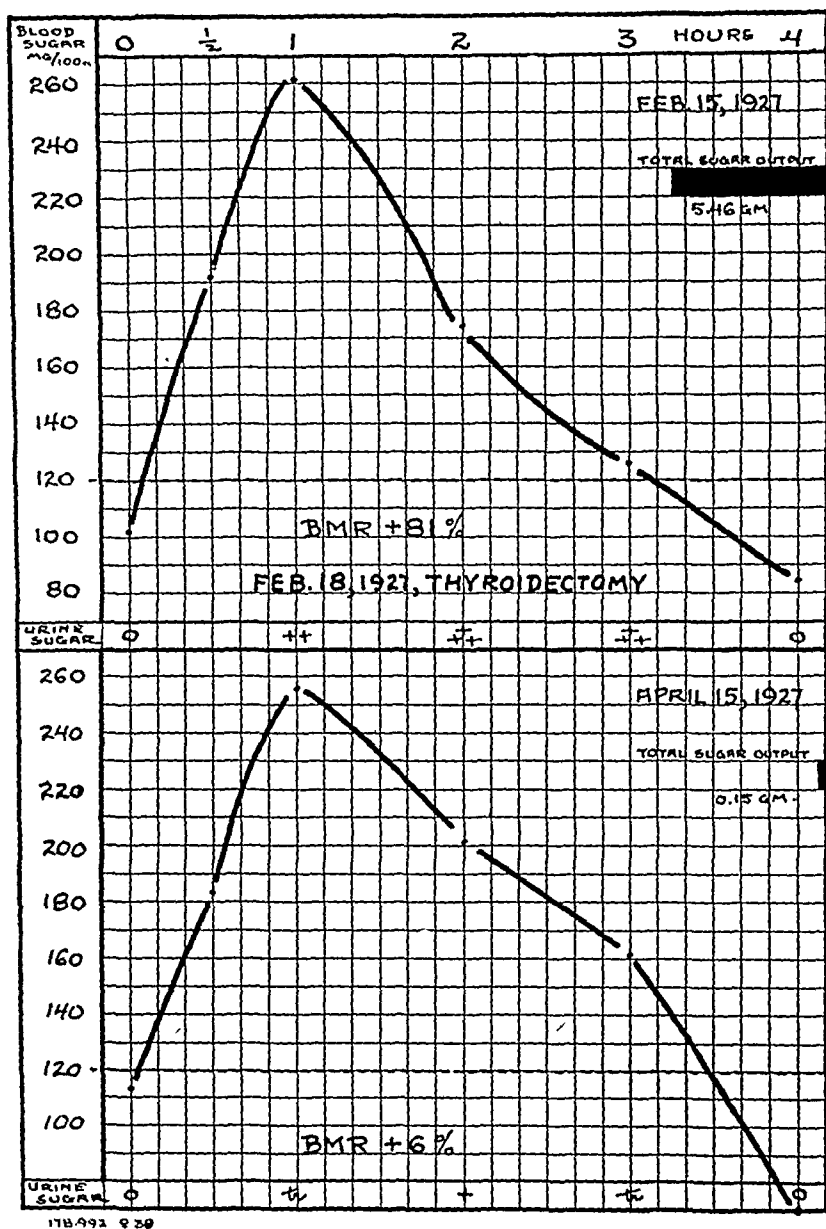


Figure IX. Charts showing findings in two glucose tolerance tests made in the same case, the first before thyroidectomy, the second two months after thyroidectomy. Note that although the hyperglycemia is more protracted in the second test, the sugar output is decreased.

in partial thyroidectomy, not of curing the diabetes but of lessening the hypofunction of the islands of Langerhans.

Rohdenburg (4) reports an interesting case of the spontaneous disappearance of diabetes. The patient was a Russian Jew who, at the age of 30, was refused life insurance on account of glycosuria. Following this she was treated medically but was never sugar-free and she showed the classical symptoms of diabetes during this time. During the following seven years she lost 35 pounds. At the age of 40 a stormy menopause occurred. Three years before her death, with the passing of the menopause, the symptoms of diabetes disappeared, repeated examinations of the urine failed to show sugar and she was able to eat candy without the production of glycosuria. She died in coma of supposedly nephritic origin.

Autopsy revealed hypertrophy of the cardiac muscle with relative valvular insufficiency; marked chronic interstitial nephritis; cystic degeneration of the adrenal glands; fibrotic ovaries; diffuse arteriosclerosis, most marked in the aorta. The thyroid gland showed almost complete destruction of the secreting alveoli and their replacement by connective tissue richly infiltrated with round cells. The head of the pancreas showed marked fibrosis, most of the glandular elements being destroyed and only an occasional island of Langerhans persisting. In the body of the pancreas there was a marked hypertrophy of the islands of Langerhans, most of these being three or four times their usual size. The tail of the pancreas showed no change. These findings in the thyroid and pancreas, in the light of the clinical history, are extremely significant.

The author says that he has seen a similar hypertrophy of the islands of Langerhans in a case of carcinoma of the head of the pancreas associated with Addison's disease, in which both of the adrenal glands had been completely destroyed by tuberculosis. In this case the hypertrophy was chiefly in the body of the pancreas.

Marinesco and Parhon (5) state that removal of the pancreas is followed by signs of over-function of the thyroid gland and that removal of the thyroid is followed by hypertrophy of the islands of Langerhans. Similar changes in the islands have also been reported by Falta (6) and by Lorand (7). Accord-

ing to Allen (2) the observations of these authors await further confirmation.

Garrod (8) refers to a few cases in which exophthalmic goiter was associated with atrophy or other lesions of the pancreas.

The Relation of the Thyroid Gland to Blood Sugar and Glycosuria. Many investigators offer observations on the relationship of hyperthyroidism to blood sugar.

Lüttichau (9) found that athyroidism in animals causes a slight diminution of the blood sugar. Hyperthyroidism produced by thyroid extract, on the other hand, causes a relative hyperglycemia.

Lund and Richardson (10) made blood sugar estimations before and after operations on the thyroid in 29 cases. They found that in patients with hyperthyroidism the blood sugar rose after operation, this rise being similar in every way to that occurring in the other patients. Hypoglycemia did not occur in any case.

Massa (11) found that both in rabbits and in man the blood sugar rose after the application of diathermy to the thyroid region. In exophthalmic goiter this procedure caused a rise which the author explains as probably due to different (sympathicotonic and vagotonic) types of the disease.

Rosenberg (12) studied the glucose tolerance by administering 100 grams of dextrose dissolved in 300 cc. of caffeineless coffee substitute, two hours after breakfast. He found that in cases of Graves's disease the glucose tolerance curves were not regular, being normal in several cases, while in others they resembled a diabetic curve. He thinks that the alterations in the curves do not run parallel to the gravity of the clinical symptoms of hyperthyroidism. Sugar excretion also seemed to be increased in Graves's disease.

Gardiner-Hill *et al.* (13) state that in exophthalmic goiter the blood sugar curves tend to be high and prolonged and that glycosuria is usually present. On the other hand, in 15 well marked cases of myxedema the blood sugar curves were higher and more prolonged than in normal persons. Glycosuria was rarely present. These authors suggest that in myxedema the renal threshold is raised.

Marks (14) noted a secondary hyperglycemia following the

injection of glucose or of small doses of insulin into thyroid-fed rabbits whose livers contained glycogen, but when the liver glycogen was depleted a small dose of insulin or an injection of glucose produced a fatal hypoglycemia.

Waldorp and Trelles (15) found a high degree of glycemia in nine of 19 patients with thyroid disease associated with a high basal metabolism.

San Martin (16) states that the thyroid gland has a special influence on the carbohydrate metabolism and that hyperthyroidism is frequently accompanied by hyperglycemia and even by glycosuria. In hypothyroidism, myxedema and cretinism, on the other hand, the tolerance for carbohydrate is greatly increased. Following the extirpation of the thyroid, the parathyroids being left intact, glycosuria, according to the author, never occurs even after the ingestion of large quantities of sugar. The author has observed two classes of diabetic patients with impaired thyroids: those in whom the diabetes antedated the manifestations of hyperthyroidism and those in whom the signs of Basedow's disease appeared before those of diabetes. He concludes that hyperthyroidism plays a fundamental etiologic rôle in the disturbance of endocrine equilibrium which constitutes the diabetic syndrome.

Experimental work on the effect of thyroxin on the blood sugar is reported by Bodansky (17), who administered thyroxin subcutaneously to sheep and noted a subsequent rise of blood sugar. Small and consistent but temporary increases in the blood sugar were observed soon after single injections. When thyroxin was administered every other day larger increases were observed after variable latent periods. The blood sugar did not stay at a uniformly high level, but wide fluctuations were observed. In thyroidectomized sheep the average blood sugar level was raised only during the first weeks of treatment with thyroxin, when the animals were on an adequate diet and when the blood sugar was taken after a morning in the pasture. During this period the fasting blood sugar would probably have been raised by thyroxin at the expense of the store of glycogen present in the liver at the beginning of the experiment. The fasting blood sugar in the cretin sheep, the glycogen reserve of which had presumably been partly depleted by three months treatment with thyroxin, was about 50 mgm. per 100 cc., a value

similar to that found in untreated cretins. Increased doses of thyroxin produced fluctuations of the blood sugar, the range being between 40 and 60 mgm. per 100 cc., a low range even for a cretin. The "fasting" blood sugar of normal sheep was raised by thyroxin, presumably at the expense of the glycogen store.

Hancher *et al.* (18) administered orally to 32 dogs a glycerol extract of hashed thyroid glands of pigs and produced a marked and sustained rise in the blood sugar. This effect was

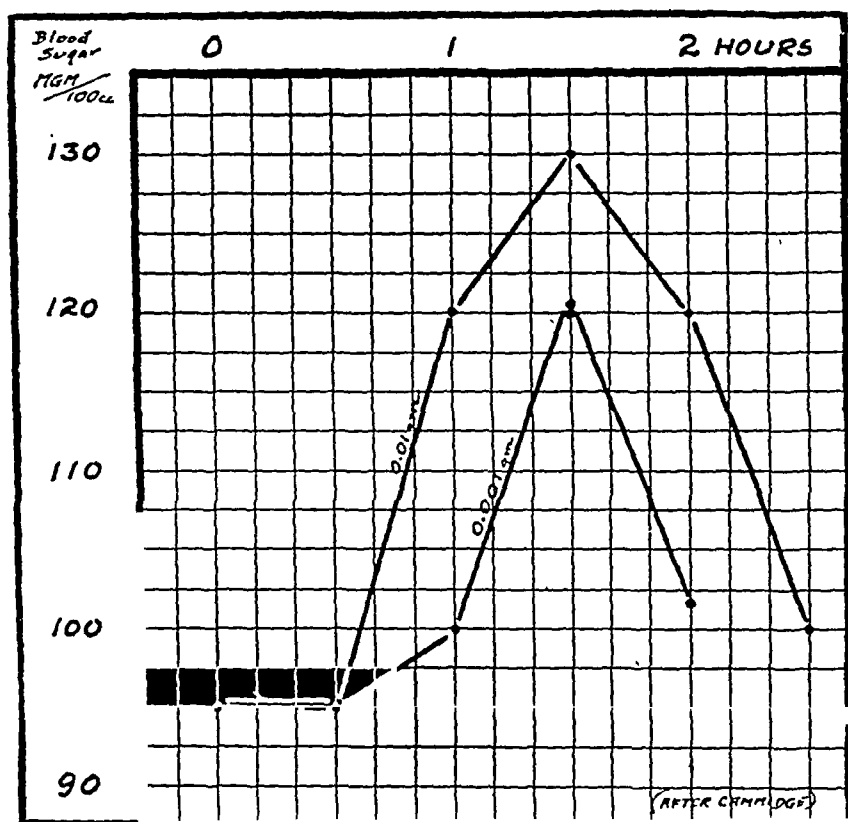


Figure X. Chart showing the rise of blood sugar in a rabbit following the administration of thyroid extract in varying doses. (Plotted from data reported by Cammidge.)

not produced when any of four commonly used commercial preparations of the thyroid gland were administered; one of these, in fact, caused an immediate and distinct decrease in the blood sugar.

Geyelin (19) reports cases of myxedema which showed a

distinct hypoglycemia with blood sugar values as low as 53 and 68 mgm. per 100 cc. Janney and Isaacson (20) had two mild cases of myxedema in which the blood sugar was normal but the glucose tolerance curve was prolonged.

According to Bang (21), glycosuria often follows the administration of thyroid extract and of hypophysis cerebri (dry powder), though not constantly. He states also that the reverse condition, namely, the appearance of glycosuria, takes place after the extirpation of the thyroid gland.

Falta, Newburgh and Nobel (22) showed that after the extirpation of the thyroid gland the injection of adrenalin does not cause glycosuria, but if the administration of adrenalin is combined with the administration of thyroid extract, glycosuria is produced. These authors formulated the hypothesis that the thyroid and the hypophyseal substance cause sensitization of the sympathetic complex to the physiological quantity of adrenalin in the blood.

Cambridge and Howard (23) produced a marked hyperglycemia by the injection of thyroid extract into a fasting rabbit. This hyperglycemia seemed to be directly proportional to the dose of the thyroid extract (Figure X).

Flesch (24) reported 40 cases of hyperthyroidism among which there was not a single case of spontaneous hyperglycemia.

In a study of 27 cases of hyperthyroidism, Geyelin (19) found hyperglycemia in 90 per cent of the moderate and severe cases and even in the mild cases an alimentary hyperglycemia (two hours after the ingestion of 100 grams of glucose) could frequently be demonstrated.

Denis, Aub and Minot (25) made glucose tolerance tests in cases of hyperthyroidism, using normal individuals as controls. In 16 normal subjects—seven females, nine males—their findings ranged as follows:

Fasting Blood Sugar*		Blood sugar after ingestion of glucose, 100 gm.; bread, 50 gm.; butter, 20 gm.		
		1 hr.	2 hrs.	4 hrs.
Lowest	90	86	84	86
Highest	120	140	120	122

*Blood sugar values in mgm. per 100 cc.

In the 31 cases of hyperthyroidism the blood sugar ranged as follows:

	Fasting Blood Sug.*	Blood sugar after ingestion of glucose, 100 gm.; bread, 50 gm.; butter, 20 gm.			
		1 hr.	2 hrs.	3 hrs.	4 hrs.
Lowest	80	90	97	120	69
Highest	133	232	220	153	140

*Blood sugar values in mgm. per 100 cc.

Among the cases of hyperthyroidism, fasting glycosuria was present in only one; it was questionable in another. The basal metabolism ranged from plus seven to plus 100 per cent. These authors state that there is no definite relationship between the severity of the hyperthyroidism, as expressed by the increased basal metabolic rate, and the degree of alimentary hyperglycemia or glycosuria. In a number of cases in which the tolerance test was repeated after the condition of the patient had been improved by rest and by operation they found that the alimentary hyperglycemia produced by the test meal was less severe than in the first test. They call attention to the possibility of emotional hyperglycemia and glycosuria in hyperthyroidism, as this condition offers notorious examples of nervous instability. These authors conclude that fasting hyperglycemia is very rarely associated with hyperthyroidism but state that alimentary hyperglycemia was observed in every case examined, a statement which requires a definition of what the authors mean by "alimentary hyperglycemia," since to a certain degree this is a normal physiological response.

While these authors found that the fasting blood sugar in hyperthyroidism is within normal limits, Sainton, Schulman and Justin-Besançon (26) found a definite hyperglycemia after the ingestion of glucose or the administration of suprarenin.

Charvat (27) tested the glucose tolerance of patients with hyperthyroidism together with that of controls and reports the following results: In patients with normal thyroids there was either no change of the blood sugar level after the ingestion of glucose or else it was lowered. In cases of hyperthyroidism, on the other hand, with but one exception the blood sugar level rose. (The author does not state the amount of glucose ingested and, moreover, his observations extended for only one hour after

the glucose was ingested, so that it is hard to evaluate his figures.) In discussing his observations the author says:

"That hyperthyroidism affects the blood sugar level is certain, but what is the mechanism of this effect? Does the thyroid exert a direct influence on the sympathetics, on the liver? Or is this influence exerted via the suprarenals? We need not imagine that the increased function of the thyroid (according to the well known diagram of Falta) causes an increased output of adrenalin, for an increased blood sugar is not associated with the glycosuria of hyperthyroidism."

May this correlation perhaps be explained by the fact that thyroid extract sensitizes the liver to adrenalin? The influence of the thyroid might also be exerted via the pancreas. Again and again sclerosis of the islands of Langerhans has been described as present in cases of hyperthyroidism following the extirpation of the gland, and in cases of myxedema, on the other hand, these islands are enlarged. Bodansky (28) produced hypoglycemia by the injection of thyroxin so that we can not rule out this last possibility.

Richardson (29) says that "some patients with exophthalmic goiter are known to respond to the ingestion of glucose by excreting sugar in the urine, and this might be taken as evidence that they are partially diabetic. Observation shows, however, that our patient was able to oxidize the glucose to the same extent as the normal individual."

In 1920 Rohdenburg (3) described two such cases of thyroid diabetes in which glycosuria disappeared after the removal of a portion of the thyroid gland. One of these patients was still sugar-free several years later on a very liberal diet.

Gardiner-Hill et al. (13) in making tolerance tests in a series of 15 well marked cases of myxedema, found decreased tolerance in some, but rarely found glycosuria; they conclude that the renal threshold is raised in this condition. One can not speak of a raised renal threshold in these cases, for it is impossible to interpret the absence of glycosuria during a glucose tolerance test. The probable reason why no glycosuria was observed is the fact that in myxedema the carbohydrate tolerance is increased so that the blood sugar level is raised but little, and even though the renal threshold may lie somewhere between 140 and 180, this level is not reached; consequently there is no justification for the above cited opinion.

Sanger and Hun (30) made glucose tolerance tests, measured the respiratory quotient and calculated the number of grams of carbohydrate utilized in a series of ten cases of hyperthyroidism. Their statement that "it has been shown that in hyperthyroidism, sugar, when it is offered to the tissues as a fuel, is burned with great avidity," seems contrary to my own conception, as does their claim that "the increased utilization of carbohydrate after carbohydrate ingestion, along with the maintained high blood sugar, points toward an inability to store glucose—most probably a failure of liver storage, due to some toxic change in the liver caused by the disease."

To take up the latter problem, it has been shown that a derangement of the liver or even the elimination of the liver does not produce a rise of blood sugar but rather a fall; in fact, fatal hypoglycemia follows complete hepatectomy. Thus, although one might reason *a priori* that when the liver is unable to store glucose the unstored amount would remain in the circulation and thus bring about hyperglycemia, experimental evidence does not support this assumption, since the storage in the muscles is probably increased as the storage function of the liver is diminished. I cannot but feel that a protracted hyperglycemia after the ingestion of a large dose of carbohydrate means that the body is unable to supply insulin in sufficient quantity to transform this carbohydrate into glycogen to be stored in the liver and the muscles, and to bring about its proper oxidation. It has been shown that the stores of glycogen are depleted in hyperthyroidism. Is this depletion due to some interference with the storage of glycogen, as these authors claim, or does it occur because the glycogen has been drawn upon too heavily on account of the markedly increased basal metabolic rate and the consequent increased oxidation of glucose in the body? Hyperglycemia is the result of faulty oxidation of glucose, for we do not find it in many cases in which the basal metabolic rate is high, in which surely the liver glycogen is depleted, but nevertheless the blood sugar remains at the normal level.

These authors have shown by their figures that in a case of hyperthyroidism sugar is burned at a more rapid rate than in a normal individual. This one would expect, for if the total oxidation of the body is increased in cases of hyperthyroidism, as

is shown by the high metabolic rate, then the rate of combustion of carbohydrate must also be increased. Moreover, this higher rate of combustion of carbohydrate will continue until the islands of Langerhans can no longer supply a sufficient quantity of insulin to cope with the increased demand. In other words, in hyperthyroidism there is a hyper-secretion of insulin which lasts as long as the islands of Langerhans can stand the demand on them. In the early stage of hyperthyroidism, as is stated by these authors, there is only this increased metabolic function, a sort of last rush of flames before the fire dies down. Carbohydrate (and protein and fat as well) are burning with a greater intensity, as the R.Q. curve shows, the R.Q. falling only at a later stage when the islands are becoming exhausted and are no longer able to supply a sufficient amount of insulin. This, I think, can be seen from the data given by these authors, from which I have constructed the curves shown in the charts in Figure XI. Thus, for instance, if charts 9, 10, 17, 18 and 20, in which the height and the protraction of the blood sugar curves are but slight, are compared with curves 7, 8 and 16, this relationship can be noted. In other words, the more nearly the blood sugar curve simulates the curve which is characteristic of severe diabetes, the lower the R.Q. curve. I think it is rather hard to interpret the early findings in the borderline cases in which the insulogenic function is not very much reduced. A clear-cut interpretation can be secured only from extreme cases at both ends of the line, on the basis of which the relationships in the cases lying between the two extremes can be interpreted.

Glycosuria and Hyperglycemia Induced by the Ingestion of Thyroid Extract. That the administration of thyroid extract is apt to produce glycosuria is well known. In such a case the glycosuria indicates the presence of hyperglycemia, the degree of which depends in part on the renal threshold of the individual for glucose and in part on an increased toxic permeability of the renal filter. Sometimes, if the thyroid feeding is continued long enough, one can note the same effects as those produced by hyperthyroidism, namely, a higher and a more prolonged rise in the glucose tolerance curve—a type of curve such as characterizes a mild stage of diabetes, or the so-called “functional diabetes.”

Von Noorden (31) is of the opinion that thyroid feeding elicits the presence of a prediabetic condition. Glycosuria and the accompanying hyperglycemia, however, are not in evidence in all cases. Thus Becker (32) reports the case of a boy two and one-half years of age who ate 90 tablets of thyroid extract at one time but did not show glycosuria.

On the other hand, Garrod (8) speaks of a youth 18 years of age who probably had no thyroid inadequacy, but after he had taken five grams of thyroid extract daily for about six weeks glycosuria developed. When the drug was stopped the glycosuria promptly disappeared. In another case in which thyroid extract was taken to reduce obesity, at the end of a week sugar appeared in the urine to the amount of four per cent, although only four grams of the thyroid extract had been taken. The glycosuria quickly disappeared after the medication was discontinued. Garrod observed a like result in cases of myxedema which had been treated with thyroid extract. Among 11 myxedematous patients four were found to have glycosuria, and in three of these cases the glycosuria disappeared within a week after the administration of the thyroid extract was discontinued.

In Notthafft's (33) remarkable case (cited by Garrod), a man 43 years of age, on his own initiative, in order to reduce his weight, took about 1000 five grain tablets of thyroid extract in the course of five weeks. Glycosuria was induced and in association with it there appeared the symptoms of Graves's disease—tachycardia, exophthalmos with von Graefe's sign, tremor, and even some enlargement of the thyroid gland. He passed daily over 3000 cc. of urine which contained one per cent of sugar (total excretion of sugar—30 grams). Without any limitation of the carbohydrate intake, the sugar disappeared and thirst ceased after the drug had been discontinued for ten days. Tremor ceased some four weeks later, but the eye phenomena and the swelling of the thyroid gland persisted for about six months.

We may consider such a case as this as one of functional diabetes, since it is accompanied by all the symptoms of early diabetes, viz., thirst, hyperglycemia, glycosuria and polyuria. As soon as the exciting cause, the ingestion of thyroid extract,

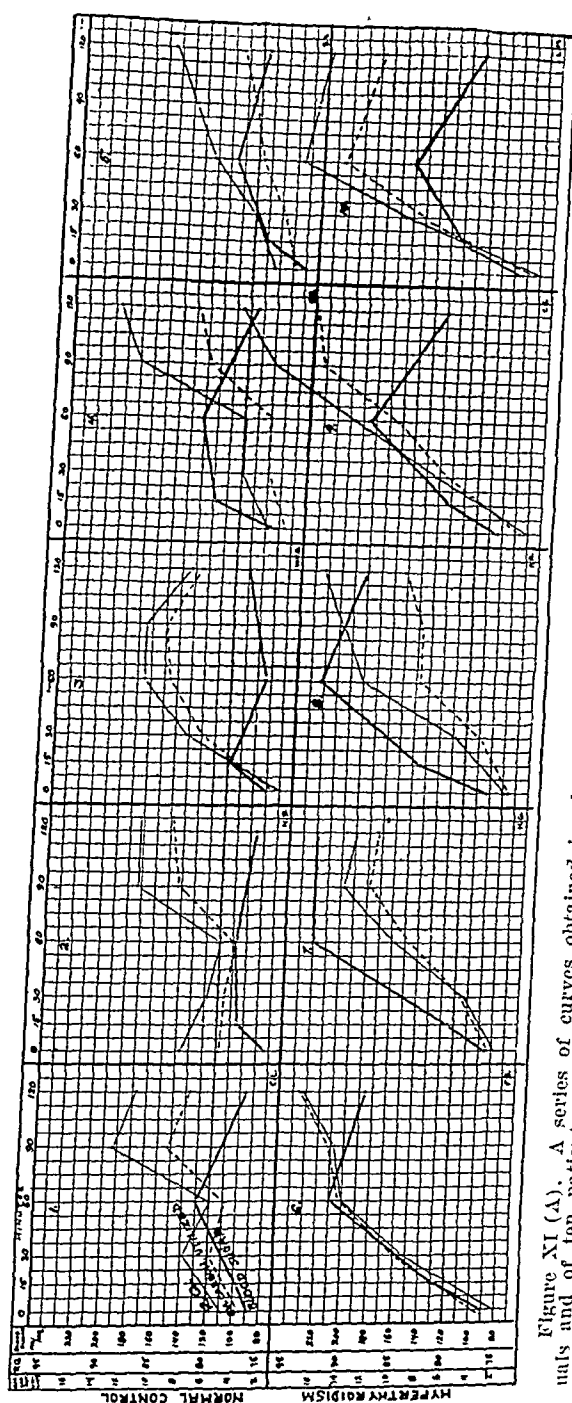
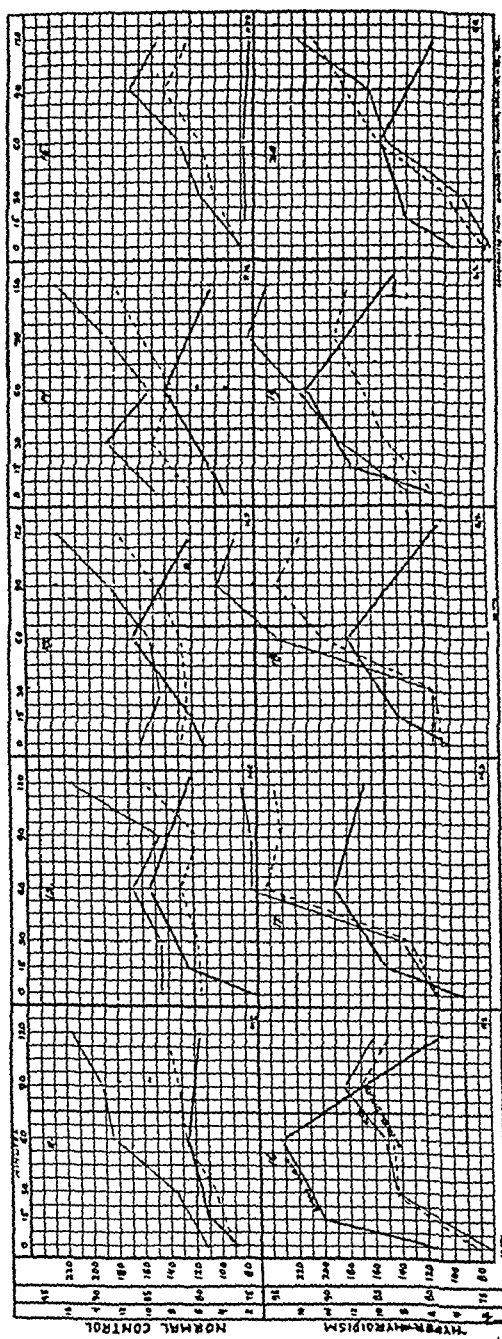


Figure XI (A). A series of curves obtained in glucose tolerance tests made in the cases of ten normal individuals and of ten patients with hyperthyroidism, with synchronous R. Q. determinations and carbohydrate utilization curves. (Plotted from data reported by Sanger and Hun.)



is eliminated, just as when the thyroid gland is eliminated in a case of active hyperthyroidism, the symptoms subside because the islands of Langerhans are not permanently damaged. It is hard to explain such cases by the assumption that in hyperthyroidism the blood contains an over-supply of glucose, when we know that in these cases the liver is glycogen-poor or glycogen-free. Where then would the superabundant sugar come from? The increased postprandial hyperglycemia which occurs in these cases can be explained only by the assumption that the liver of an individual with hyperthyroidism can not properly store glycogen. But as the liver becomes glycogen-poor or glycogen-free, it would appear that a vacuum for postprandial storage should be present. Why then does not such storage take place? Is it because of the lack of insulin? Or does the toxicity of the hyperthyroidism *per se* make the liver cells less able to perform their proper function of glycogen storage? Either of these suggestions would supply a suitable explanation—but that the hyperthyroidism is due to hyper-production of blood sugar does not seem to fit the existing conditions. If there were such hyper-production then this should be most marked in the most severe cases. But such is not the case, at least according to my observations in a large series of severe cases in which the carbohydrate tolerance has been perfectly normal; while, on the other hand, in many a case of mild hyperthyroidism there is a severe derangement of carbohydrate metabolism. If this derangement is due to intoxication affecting the liver, these mild cases should show only a slight carbohydrate disturbance. Consequently, I feel that we must look for the cause of the hyperglycemia in the reserve in the islands of Langerhans in the individual case, a small reserve being easily exhausted, a large reserve resisting even severe hyperthyroidism.

For practical purposes I feel we can consider that the effects of thyroid feeding and of hyperthyroidism are the same. Thyroid feeding therefore gives us an excellent opportunity for the investigation of the effects of hyperthyroidism. Perhaps by persistent experiments with thyroid feeding and by continued clinical observations we may be able to discover whether hyperthyroidism also affects a perfectly normal insulogenic reserve.

This is a practical question. Until recently, I had the feel-

ing that the tolerance of a person with a good insulogenic reserve, as shown by a normal glucose tolerance curve, could not be broken down. Today I feel that I can not make any such positive statement. More data are needed in order that we may see how frequently the exceptions to this conception occur. I can review at least one case in which thyroid feeding did affect and break down a normal tolerance.

Case I (164227): This patient was a married woman 28 years of age. On March 23, 1926, she came to the Clinic because of obesity and shortness of breath. The only significant fact elicited in the family history was that two sisters were stout. She had had none of the usual diseases of childhood, but had had tonsillitis, frequent colds and rheumatism later in life. A curettage had been done in 1917 and tonsil-adenoidectomy in 1923. In 1924 she had a tubal pregnancy and she had had five or six miscarriages. Her weight in 1918 was 105 pounds. (The normal weight for her height, 5 ft. $\frac{1}{2}$ in., would be 118 pounds.) When I saw her she weighed 233 pounds, hence was 97 per cent overweight. Her feet were swollen at times and she had frequent suboccipital headaches.

The only pertinent findings in the physical examination were the following: Blood pressure, 144/90; pulse, 92; visual fields, normal, and no pathological conditions in the retina. The urine showed a faint trace of albumin but no sugar on several examinations. The blood Wassermann test was negative. The blood chemistry findings were: Sugar, 95; urea, 33; uric acid, 4.2; creatinin, 1.3; non-protein nitrogen, 41.3, and plasma chlorids, 615 mgm. per 100 cc.

During the preceding eight years the patient had increased in weight from 105 to 233 pounds, and during the last three years of this period she had gained 80 pounds. The problem was to decide whether or not we could safely reduce her weight by the usual routine, including the administration of thyroid extract. Thus on March 24, 1926, I made a glucose tolerance estimation which gave a normal curve (see Figure XII—A), and showed that the renal threshold lay above 180 mgm. per 100 cc. The basal metabolic rate at this time was plus 12 per cent, so that it was at the upper normal limit. With these data it seemed safe to institute reducing measures and the administration of five grains of desiccated thyroid substance three times a day was started in April, 1926, and was continued for four months, being discontinued in August because of a rapid pulse. During this time there had been a very slight reduction in weight—from 233 to 228.5 lbs. The patient was seen again in the latter part of November, at which time definite symptoms of hyperthyroidism were present, and the basal metabolic rate was plus 24 per cent. At this time (November 29, 1926) a glucose tolerance test (see Figure XII—B) showed a definitely de-

creased tolerance as compared with the tolerance at the time of the previous examination, and the renal threshold lay above 236 mgm. per 100 cc., which is contrary to the usual finding in hyperthyroidism.

Thyroidectomy was performed on December 8, 1926, and four months later the patient again returned. Subjectively she had improved, but the pulse rate was still elevated. Her basal metabolic rate at this time was again plus 12 per cent. I made another glucose tolerance test with the result shown in Figure XII—C, which shows a decided improvement over the diminished tolerance shown in B. Her weight had remained the same. An x-ray examination at this time again failed to show any enlargement of the sella turcica.

In brief, in this case the feeding of thyroid substance induced a state of hyperthyroidism which, in turn, produced an early diabetic condition—functional diabetes—so that thyroidectomy had to be resorted to in order to eliminate both the hyperthyroidism and the functional diabetic state.

One can hardly doubt that in this case a state of hyperthyroidism was precipitated by the thyroid medication; furthermore, the glucose tolerance definitely decreased. One can not blame this diminished tolerance on the obesity, for we know that in the course of the preceding eight years the obesity had not lowered the carbohydrate tolerance. Nor can her diet be blamed, as during the period of thyroid administration she was on a minimal diet. This case emphasizes clearly the importance of exercising extreme care in the use of thyroid medication. There is little doubt in this case that had the administration of thyroid substance gone on, a definite diabetic state would finally have been induced.

The Relation of Iodin to Carbohydrate Metabolism in Hyperthyroidism. In 1920 Labbé (34) (cited by Wilder), noted that in cases of diabetes complicated by frank exophthalmic goiter, iodine has a beneficial effect not only on the intensity of the diabetic process but on the exophthalmic goiter syndrome. In Labbé's patient the excretion of sugar, which was 209 grams daily, dropped to 71 grams daily after treatment with iodine, and the palpitation and tachycardia also were favorably affected. Following the suggestion of Plummer and Boothby, in the Cleveland Clinic Hospital Lugol's solution is used in practically the same dosage as that suggested by these authors, i. e., ten minims three times a day until the maximum benefit is obtained. We have noted that the beneficial effects of this admin-

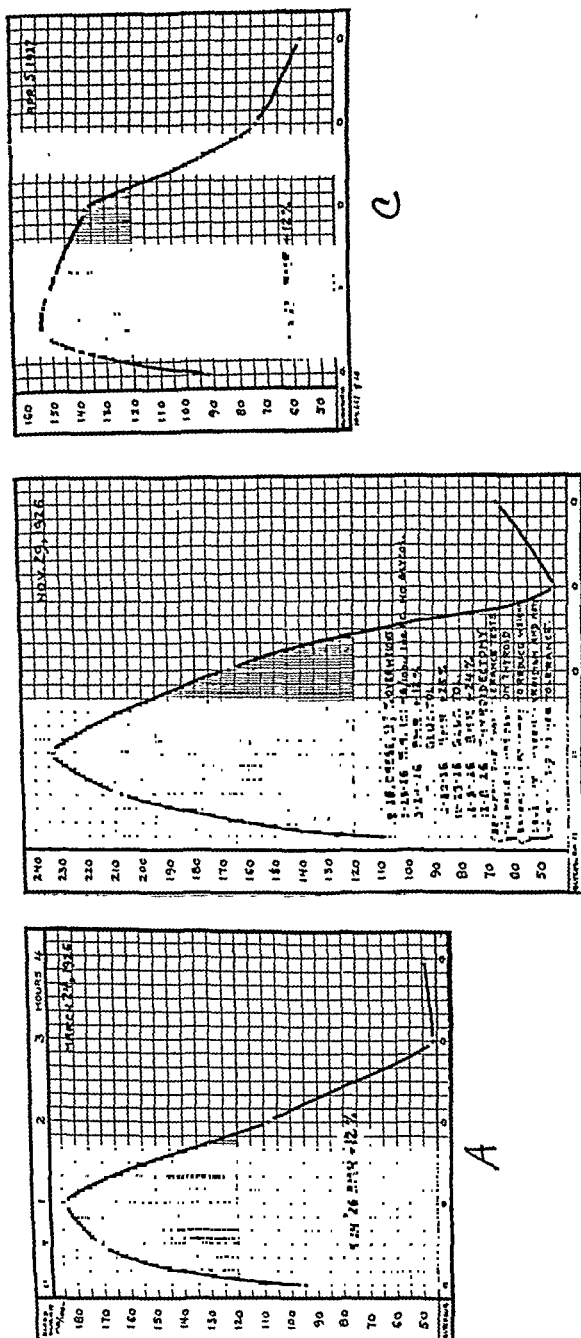


Figure XII. Three charts showing the findings in glucose tolerance tests made in the same case (Case I), the first while the patient's condition was normal except for obesity, the second after the use of thyroid extract, the third after thyroidectomy.

istration continue for from eight to ten days, when the optimum effect is reached, after which time the patient's condition retrogresses. The surgeons have learned by experience that the best time to operate is when this optimum moment has been reached.

Charvat (27) says:

"In our series of cases of hyperthyroidism the blood sugar rose after the injection of iodine and we think that in these cases this was due to an increased function of the thyroid, which was irritated by the sudden influx of iodine. The doses that we injected were so small that the patients did not react to them in any other way. We may assume that these small doses are not sufficient to stimulate a normal thyroid gland to activity. The hyperactive gland, however, is more labile, it is more sensitive to iodine and it is stimulated to specific activity for a time after the injection of iodine by a dose which does not affect a normal gland. We tried to see if by means of a larger dose we could stimulate a normal thyroid to specific action which would manifest itself by a lowering of the blood sugar level. In the single attempt thus far made this seems to be the case, but the changes were so small that they lie within the limits of experimental error.

"We think that the effect of iodine on the blood sugar level in hyperthyroidism probably goes through the following circuit: thyroid—vegetative nervous system—liver. That the liver reacts to stimulation of the sympathetic and parasympathetic nervous systems by the production of glycemia is well known [Bornstein and Holm (35)]. We also know that all substances which can call forth the thyroid effect lead to the washing-out of liver glycogen until it disappears [Abderhalden and Schiffmann (36), Romeis (37)]. That the thyroid has other direct connections with the liver is clear from the experiments of Leone (38), who noted marked changes of the bile (decrease of salts, cholesterolin, urea, etc.) after the subcutaneous or the oral administration of thyroid extract to a dog with a gall-bladder fistula. We think further that the mobilization of liver glycogen through the influence of the thyroid gland is not a hormonal process but takes place via the vegetative nervous system, for the changes in the blood sugar level are of short duration and soon disappear."

The effect of the iodine on carbohydrate metabolism is probably a secondary one, that is, the lessening of the hyperthyroidism lessens the total metabolism, which, in turn, lifts part of the extra load off the islands of Langerhans. We must remember that the protein metabolism also is high in these cases and this factor probably contributes to the diminished carbohydrate metabolism.

The Relation of Hyperthyroidism to Diabetes. The coincidence of glycosuria and even of hyperglycemia with hyperthyroidism has already been discussed briefly in a preceding section of this paper.

The earliest report on the relation of the thyroid gland to diabetes was read by Dumontpallier (39) in August, 1867, at a meeting of the Société de biologie. He cited the case of a woman, 22 years of age, with a hypertrophied thyroid, who

TABLE VIII
CASES OF COINCIDENT DIABETES AND HYPERTHYROIDISM REPORTED IN THE LITERATURE

Author	Number of Cases	Total Series of Cases of Hyperthyroidism	Outcome		Year
			Cured or Improved	Died	
Dumontpallier.....	1	1	1867
Brunton.....	1	1874
Hartmann.....	2	1878
Budde.....	2	1891
Manges.....	1	1899
Müller.....	2	1906
Thompson.....	3	80	1906
Sattler.....	56	From literature	..	25	1909
Crile.....	1	..	1	..	1915
O'Day.....	4	..	4	..	1916-20
Rohdenburg.....	2	..	2	..	1920
Fitz.....	9	1800 (Mayo Cl.) 315 (M. G. H.)	1921
Holst.....	10 (glycos.)	..	10 (by thyroidect.)	..	1921
Cammidge.....	1	..	1	..	1923
Buchanan.....	1	..	1	..	1924
Charvat.....	1	..	1	..	1926
John.....	40	93	91	2	1927

complained of marked pulsation of the heart. The case was undoubtedly one of Basedow's disease. Bulimia and excessive thirst had been present for several months. The patient had lost a great deal of weight, had nocturia, and glycosuria—6.2 per cent—and anemia were present. The condition improved after a dietary regimen was instituted, and the urine became less abundant but there was no remission of the symptoms of Basedow's disease. In the winter of 1867 the patient caught cold and died of inflammation of the chest.

The first case of this nature reported in the English literature was that of Landor Brunton (40) in 1874. Hartmann (41) reported two cases from the Tübingen Clinic in 1878. Budde (42) reported two cases in Denmark in 1891, and in 1899 Manges

(43) of New York offered the first report in the American literature.

Von Noorden many years ago described what he termed thyroid diabetes and others [Jacobson (44), Williams and Humphreys (45), Hamman and Hirschmann (46), Hopkins (47), Taylor and Hulton (48), McCaskey (49)], have emphasized the relationship. McCaskey, who investigated the glucose tolerance in some 30 odd cases of exophthalmic goiter, was unable to demonstrate a specific curve of glucose tolerance in the blood during the disease, although he, with others, noticed that there was a slight fasting hyperglycemia in these cases.

In 1906, Friedrich Müller (50) suggested that a special type of glycosuria is related to exophthalmic goiter. His immediate reasons for this belief were drawn from his experience with two cases. The first of these was a case of exophthalmic goiter in which he had given thyroidin, hoping thereby to diminish the size of the thyroid gland. The symptoms of hyperthyroidism did not improve under this form of treatment and sugar began to appear in the urine in increasing amounts. Even after the administration of thyroidin was stopped, the glycosuria did not diminish, and the patient died in coma a few months later. The second case was that of a woman with a chronic goiter in whom diabetes had developed after she had taken thyroid extract for a long time. Some time later the goiter disappeared spontaneously, and, to Müller's surprise, the symptoms of diabetes also disappeared, so that the patient was eventually able to take large amounts of carbohydrate without the production of glycosuria. These two cases were the basis for Müller's statement, reported by Fitz (51), that in the future the thyroid gland should be studied more carefully in its relation to diabetes.

In 1909 Sattler (52), collected 56 reported cases in which diabetes was associated with hyperthyroidism. Thirty-seven of these cases had been followed for a sufficient length of time to afford positive information: 25 cases ended fatally within comparatively short periods of time, and in seven cases the patients died in coma. In the majority of cases the diabetes developed in the presence of a preëxistent exophthalmic goiter, although in

a few cases the incidence of the diabetes seemed to antedate the thyroid disturbance.

In 1915 Crile (53) operated on a man, aged 42 years, with diabetes, in whom, before operation, the daily output of urinary sugar averaged 95 grams. The left and right cervical sympathetic nerves were resected, the left suprarenal was removed and a partial thyroidectomy was performed. Four months later the patient had gained nine pounds in weight and the urine was remaining sugar-free on a diet containing 250 grams of carbohydrate.

In 1916 O'Day (54) reported four cases in which exophthalmic goiter was associated with diabetes. All these patients became sugar-free and recovered a practically normal carbohydrate tolerance.

In 1921 Fitz (51) reported an exhaustive study of the relationship of hyperthyroidism and diabetes based upon data collected from the records of the Massachusetts General Hospital and the Mayo Clinic. He says that this combination of diseases is relatively uncommon, but serious. At the Mayo Clinic he found only nine cases of diabetes among 1800 cases of exophthalmic goiter. If we study the time relationship of the onset of diabetes to that of the onset of the thyroid disease in Fitz's series we find the interesting data which I have accumulated in Table IX, data which demonstrate definitely the fact that thyroid disturbance generally antecedes the onset of diabetes.

TABLE IX
THE SEQUENCE IN THE ONSET OF SYMPTOMS OF HYPERTHYROIDISM AND
DIABETES MELLITUS RESPECTIVELY
(After Fitz)

Age	Sex	Duration of Goiter Symptoms	Duration of Diabetic Symptoms	Priority of Goiter Symptoms (in Years)	Amount of Sugar Excreted in 24 Hours (in Grams)
51	M	2 yrs.	1 yr. 6 mos.	6 mos.	224
32	F	10 yrs.	2 mos.	9 yrs. 8 mos.	102
49	F	35 yrs.	7 yrs.	18 yrs.	36
47	M	13 yrs.	4 yrs.	9 yrs.	450
53	F	32 yrs.	7½ mos.	31 yrs.	170
54	F	30 yrs.	6 mos.	29 yrs.	32
40	F	7½ mos.	2 mos.	5½ mos.	4%
30	F	7 yrs.	2 mos.	6 yrs. 10 mos.	161
37	F	9 yrs.	3 mos.	8 yrs. 9 mos.	100
44	M	7½ mos.	1 yr.	Reverse	12
57	F	7 yrs.	1 yr.	6 yrs.	72
53	F	40 yrs.	6 yrs.	34 yrs.	80
58	F	40 yrs.	9 yrs.	39 yrs.	30

Fitz concludes that there is no evidence that the coincidence of diabetes and hyperthyroidism is more than a chance occurrence. He believes that the severity of the diabetes in these cases tends to parallel the severity of the thyroid intoxication and that there is no reason for assuming that partial thyroidectomy alone has any curative effect on diabetes. In evaluating this final conclusion we must remember that the cases in Fitz's series were treated in the pre-insulin era.

The presence of glycosuria in cases of hyperthyroidism was described by Chvostek (55), von Noorden (56), von Strümpell (57), and Strauss (58), although these authors found the condition but infrequently. On the other hand, von Noorden has stated that spontaneous alimentary hyperglycemia in cases of hyperthyroidism occurs quite frequently. He thinks that it is absent in cases which present a frankly vagotonic character and when the sympatheticotonic phase is in the background.

In twelve cases in which the irritation involved the sympathetic and the parasympathetic systems alike, or in which the sympathetic system was particularly affected, he found fasting blood sugar values of 120-175 mgm. per 100 cc. and a rise of at least 50 per cent in the blood sugar after the ingestion of 100 grams of glucose, but in no case did he find spontaneous or alimentary glycosuria.

Chvostek (59) recognized the frequency of alimentary and spontaneous transitory glycosuria in cases of hyperthyroidism. He thinks that there is no parallelism between the severity of hyperthyroidism and the frequency and severity of the glycosuria. Glycosuria can in no way be counted as a symptom of hyperthyroidism; it merely points, he thinks, to further derangements of the nervous and the chromaffin systems and their influence on the pancreas.

"Pure hyperthyroidism in the presence of a fully normal chromaffin system and a normal pancreas," says von Noorden (60), "will rarely produce an alimentary and spontaneous-transitory glycosuria."

Flesch (24) reports that among his cases of hyperthyroidism 60.7 per cent showed alimentary hyperglycemia of varying degrees of severity; Forschbach and Severin (61), found it to be absent in the majority of their cases. Schulze (62) saw only four cases of alimentary glycosuria among 16 cases of hyperthy-

roidism after the ingestion of 100 grams of glucose (25 per cent).

Allen (63) found that in partially depancreatized dogs thyroid feeding did not aggravate diabetes; he says that no evidence was obtained that diabetes might be caused by over-activity of the thyroid function. In diabetes of moderate severity, deficiency in the thyroid function lowered the hyperglycemia and glycosuria. He concludes that there is no definite antagonism between the functions of the thyroid and the pancreas.

Allen says: "The association of the diabetes with exophthalmic goiter indicates rather plainly that no specific effect of the thyroid over-function is involved, because the association is so uncommon."

In 1912 Garrod (8) in speaking of glucose tolerance in association with hyperthyroidism made the following statement: "Undoubtedly in many cases no diminution of tolerance can be detected, but my own experience leads me to take my stand with those who hold that it is by no means an uncommon phenomenon. In not a few cases spontaneous excretion of sugar, of a transitory or intermittent kind, is observed, if carefully watched for, and in others, as I have already mentioned, persistent glycosuria, with the usual attendant symptoms which go to make up the clinical picture of diabetes."

Hamman and Hirschmann (46) report five cases of hyperthyroidism, in four of which the glucose tolerance curve was typical of diabetes, while in the other it was normal. Glycosuria was present in all five of the cases.

In one case of hyperthyroidism in a patient 52 years of age, the authors present two curves, the first secured before operation and the second one month after operation, the latter showing marked improvement in glucose tolerance.

Lund and Richardson (10) investigated the changes in the blood sugar level which follow operations on the thyroid gland, and make the following statement: "However, practically all patients with a definite elevation in basal metabolism (plus 20 or more) show this reaction" (abnormality of the tolerance curve).

I have not found this to be the case, as an examination of the glucose tolerance curves of my patients will show. In the

series of normal curves, for instance (see Table VI), high basal metabolic rates are associated with normal tolerance curves and vice versa. I hardly feel that we can make a sweeping statement about such a relationship. These two factors (a high basal metabolic rate and a decreased glucose tolerance) may be associated with each other, but, on the other hand, one cannot say that a high basal rate must carry with it a decreased tolerance.

Cambridge and Howard (64) report the case of a woman 47 years of age with a very nervous and high-strung disposition who, in 1913, had suffered from a nervous breakdown. In 1916, while in India, she had a recurrence of this trouble; her urine at that time was sugar-free. In 1917 she began to lose weight, and traces of sugar were discovered in her urine. Her diet was reduced and she was given opiates. The glycosuria subsided and she was allowed to return to a normal diet. In 1918 she had another nervous breakdown, and typical signs and symptoms of exophthalmic goiter developed. While she was being treated for this trouble she was found to be passing large amounts of sugar in her urine and was placed on the "Allen treatment." On the second day of this treatment she became comatose and was unconscious for three days. Eventually the glycosuria ceased and, after three months in the hospital, she was sent home on a restricted diet, free from sugar. In March, 1919, she returned to England and shortly afterward her urine again showed sugar and she resumed her strict diet. For a while she was sugar-free, but later glycosuria returned. In 1920 Cambridge saw her. At that time she had all the characteristic signs of exophthalmic goiter, but there was no polyuria nor thirst. Examination of a twenty-four hour specimen of urine, while she was on a diet of 90 grams carbohydrate, gave the following findings: protein, 85 grams; fat, 80 grams; sugar, 70 grams; no acetone; creatinin, 4.4; amino-acid nitrogen, 0.5; total nitrogen, 19 mgm. per 100 cc. A serial analysis of the patient's blood made on this date after a test breakfast is presented in Figure XIII. This shows fasting hyperglycemia and the curve indicates diabetes, as does, in fact, the fasting blood sugar. Cambridge thinks that "the subsequent concurrent course of the difference value and sugar curves was in favor of the hyperglycemia being chiefly dependent upon disturbance of the func-

tions of the other ductless glands or of the nervous system, and in view of the clinical signs, it seemed likely that the thyroid was mainly at fault." Glycosuria diminished as the diet was diminished until the patient again became sugar-free. The diet was finally raised to carbohydrate, 60 grams; protein, 60-65 grams; fat, 90 grams. On this she maintained her weight and the urine remained sugar-free. She was last seen in March, 1921, up to which time she had had no glycosuria; at this time her blood sugar, two hours after a meal, was 160 mgm. per 100 cc. The authors say nothing as to the further development or subsidence of the hyperthyroidism.

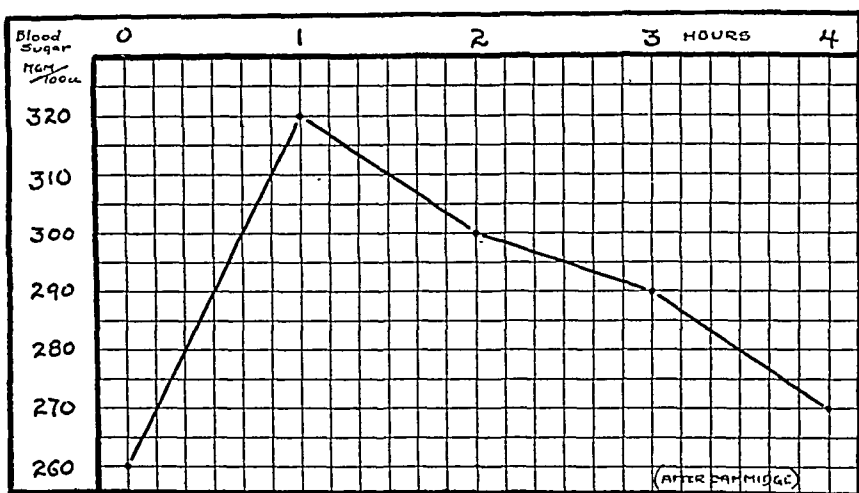


Figure XIII. Chart showing findings in a glucose tolerance test in a case of hyperthyroidism reported by Cammidge.

We have here a case of diabetes, the onset of which was preceded by hyperthyroidism, if we may consider the nervous breakdown to have been the beginning of hyperthyroidism, as the later course of events appears to prove was the case. Diabetes does not cause hyperthyroidism, but hyperthyroidism can, and I believe always does, bring to light a latent form of diabetes.

As for the incidence of diabetes associated with hyperthyroidism, but few figures are available. Sattler (52) found diabetes in three per cent of his series of cases of hyperthyroidism (in two-thirds of these cases the hyperthyroidism preceded the onset of the diabetes). Among 1000 cases of diabetes von Noor-

den (65) found 6 cases of frank hyperthyroidism and from 20 to 25 cases in which symptoms of hyperthyroidism appeared.

According to von Noorden the prognosis of these cases is poor. Sattler cites a mortality of 60 per cent among his cases of hyperthyroidism with diabetes.

Von Noorden mentions also the marked cardiac weakness in this combination of diseases, this being much more marked than is the case in uncomplicated cases of either diabetes or hyperthyroidism.

In hyperthyroidism, sweating (vagotonic) is a frequent symptom; it is absent in the less frequent sympathicotonic form. Grawitz (66) pointed out that this symptom often is absent when hyperthyroidism is combined with diabetes.

Von Noorden (67) says:

"Whether a thyrotoxic weakening of the pancreas hormone is present or whether the thyrotoxic excitation of the chromaffin system is the cause of the hyperglycemia need not be determined; the latter explanation is, after all, improbable, since the sensitivity of the liver cells to hyperadrenalism becomes greatly weakened if the latter condition is of long duration. The findings of W. Cramer and R. A. Krause seem to show that thyrotoxic influences are really determinative: In their experiments, when the animals were fed with fresh thyroid gland substance the livers became practically free from glycogen after a few days."

It seems from the above that hyperthyroidism favors glycolysis. In the animal experiments this is quite definitely proven to be the case. In man the regulatory mechanism plays a part, when the irritability of the sympathetic and of the parasympathetic systems work in harmony; the greater the irritability of the sympathetic, the lighter the disturbance of the sugar output and vice versa. In hyperthyroidism, however, according to von Noorden, we deal but rarely with a pure hyperthyreosis. We can consider it as certain that frequently functional disturbances of other endocrine organs are concerned in the production of this syndrome, and because of their interrelationship and influence on the pancreas and on the chromaffin system the primary irritation from the hyperactivity of the thyroid must have a definite influence on the sugar-forming function of the liver.

Von Noorden (68) summarizes the relationship of the thyroid gland to carbohydrate metabolism as follows:

"1. After the administration of thyroid gland by mouth or by subcutaneous injection (in rabbits or dogs), glycosuria appears frequently. This disappears after the administration of the thyroid gland is discontinued. Similar observations have been made in man, although all observers have been struck by the fact that the reaction of the human organism differs according to the individual. In some human cases a lasting glycosuria appeared after a brief period of feeding with thyroid extract (true diabetes); it is possible that in these cases there was a prediabetic condition which was first discovered after the feeding (von Noorden).

"2. In many non-diabetic individuals tests for alimentary glycosuria give positive findings after thyroid feeding, whereas they give negative findings before the feeding. Even if no glycosuria is produced, hyperglycemia usually develops (my own experiments) and in animal experiments the glycogen disappears from the liver.

"3. When thyroid substance is administered to diabetic individuals, their glycosuria is increased: This, however, is noticeable only in light cases; in severe cases the difference is too slight to be significant. The blood pressure rises at the same time (Falta), which is not the case when thyroid substance is fed to non-diabetic individuals. This is probably due to an irritation of the chromaffin system which in many diabetic patients is in a state of hyperirritability.

"4. In Basedow's disease (hyperthyroidism) the assimilation level for glucose is frequently lowered. A considerable degree of glycosuria may appear after the ingestion of 100 grams of glucose (10-15 grams). According to Eppinger, in cases of hyperthyroidism in which the signs of an increased sympathetic irritability are present one can expect to find glycosuria, whereas in those cases which present signs of more marked vagus irritability alimentary glycosuria is not present.

"5. In dogs after thyroidectomy the assimilation level for glucose is very high and the subcutaneous injection of adrenalin in quantities which under normal conditions produce glycosuria is without effect. A heavy carbohydrate intake also fails to produce glycosuria. The animals will present glycosuria, however, if, together with the injection of adrenalin, a thyroid substance is injected (Eppinger, Falta, Rudinger). Other authors (Underhill, Hilditch, Bøe, Blum) failed to confirm these findings and their observations deny any connection between the thyroid gland and carbohydrate metabolism. Nevertheless, it does not follow that we should disregard the investigations of Eppinger and his assistants, which were doubtless carried out with the greatest care. In my opinion they continue to be valid and the divergent results of the later tests must be explained. . . . If the parathyroids are removed or injured, tetany (frank or latent) is produced, on the one hand, and a considerably lowered level of the assimilation of carbohydrate on the other (Hirsch, Un-

derhill, Saiki). In this respect the action of the thyroid and of the parathyroids is antagonistic, and when both are removed the effect of the removal of the latter predominates.

"6. In the diseases of myxedema (hypothyroidism and dysthyroidism) the assimilation level for glucose is raised (Hirschl, Knöpfmacher, Ewald, Aschenheim). . . . In one case, recently observed, 250 grams of glucose were taken within about half an hour, and 250 grams of bread one hour later, but no glycosuria occurred. (N. B.—Such cases have an abnormally high tolerance for carbohydrate.) In three cases of marked thyrogenic adiposity in children from 12 to 14 years of age the fasting blood sugar values were 60-70 mgm. per 100 cc. . . . [See also John (69): 'Glucose tolerance and its values in diagnosis,' and note the glucose tolerance curves in hypothyroidism.] One cannot expect always to find such low values. In these cases there are often changes in other endocrine glands which work antagonistically. In four cases of thyrogenic adiposity in adults the following blood sugar values were found: 106, 109, 112 and 117 mgm. per 100 cc., respectively."

The above discussion suggests that thyroid hyperglycemia is due either to increased sugar production or to decreased sugar utilization. A third factor which must be considered is the inability of the liver to store glycogen, since in hyperthyroidism the liver is either glycogen-free or glycogen-poor. If sugar production were the only factor concerned, then hyperglycemia would be more marked in the most severe cases of hyperthyroidism, that is, in those in which the basal metabolic rate is most increased, and this is not the case. The seat of the trouble, then, must be sought elsewhere, and I feel that, as in any case of persistently increased glycemia, the primary cause is a decreased insulogenic capacity of the islands of Langerhans, which, in some cases, whatever the basal metabolic rate, cannot cope with their task so that carbohydrate metabolism begins to lag.

The livers in these cases are practically free from glycogen [see Cramer and Kraus (70)], thus there should be a ready storage place for the ingested sugar which would obviate an increase in the blood sugar, but this apparently does not happen in a considerable percentage of cases. Why? Has the insulin also something to do with the storage of glycogen in the liver? Or is the glycogen burned as fast as it is formed by the increased metabolism? Perhaps both of these are factors.

Boothby and Wilder (71) point out the clinical importance of recognizing the possibility that exophthalmic goiter may be a complication in cases of diabetes in which the ordinary measures of treatment by insulin seem not to be effective.

By the intravenous injection of glucose at uniform rates Wilder and Sansum (72) have shown that, whereas in normal individuals glucose can be injected intravenously at a rate of 0.8 gram per kgm. per hour without the development of glycosuria, glycosuria may appear in patients with hyperthyroidism when only 0.6 grams or even 0.5 grams of glucose per hour per kgm. are injected. In a later communication Wilder (73) states, "All such observations show that in hyperthyroidism the rate at which the body can assimilate glucose may be disturbed; they do not prove that anything is at fault with oxidation or reduction. Therefore, they do not indicate the existence of diabetes." This statement, however, is based solely on the presence or absence of glycosuria at different rates of glucose injection and, therefore, is valid only if it can be proved that in the cases of hyperthyroidism in which glycosuria appears only the permeability of the kidney for sugar is changed. No evidence is offered on this point, as synchronous blood sugar findings are not given. Moreover, to prove this statement, it must be proved that the renal threshold in such cases is lowered. This would require knowledge of the renal threshold before and at the time the hyperthyroidism developed. As to the exact height of the blood sugar at which glycosuria occurs we can offer no general rule, since the threshold varies widely even in normal individuals. We must conclude, therefore, that if glycosuria occurs (with the exception of its occurrence in individuals with very low thresholds in whom glycosuria is practically always present) that it is due to hyperglycemia—the glycosuria being but a secondary phenomenon. That this point is actually verified by Wilder's figures is illustrated by the chart shown in Figure XIV, which I have constructed from Table 3 in his article. This chart clearly demonstrates that glycosuria occurred only in the presence of hyperglycemia. It follows that if in any case a postprandial hyperglycemia is of longer duration than normal postprandial hyperglycemia, it must be concluded that there is not enough insulin available

to oxidize or reduce and store the increased sugar in the blood, in spite of the statement by Wilder that "they do not prove that anything is at fault with oxidation or reduction."

Wilder reasons further that "there is indeed good evidence to show that the utilization of carbohydrate is actually accelerated by hyperthyroidism in patients who do not have true diabetes. Following test meals of glucose in patients with exophthalmic goiter, as DuBois (74) and also Sanger and Hun

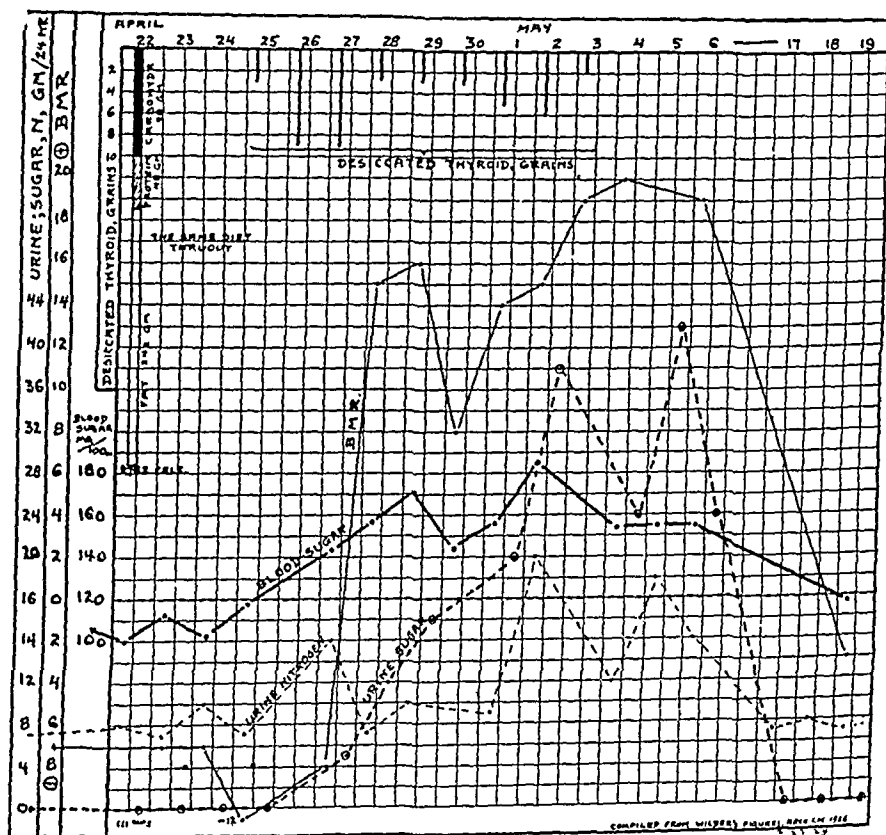


Figure XIV. Synchronous blood sugar, urine sugar and basal metabolic rate findings before and after the administration of thyroid extract. (Compiled from Wilder's figures.)

(30) have shown, the respiratory quotients rise more abruptly than is normal." This is true, but this statement has no direct bearing on the problem of the relationship of diabetes to hyperthyroidism, as in cases of non-diabetic hyperthyroidism we may assume that the insulogenic apparatus is intact and has still a large reserve whereby to cope with any situation with which it

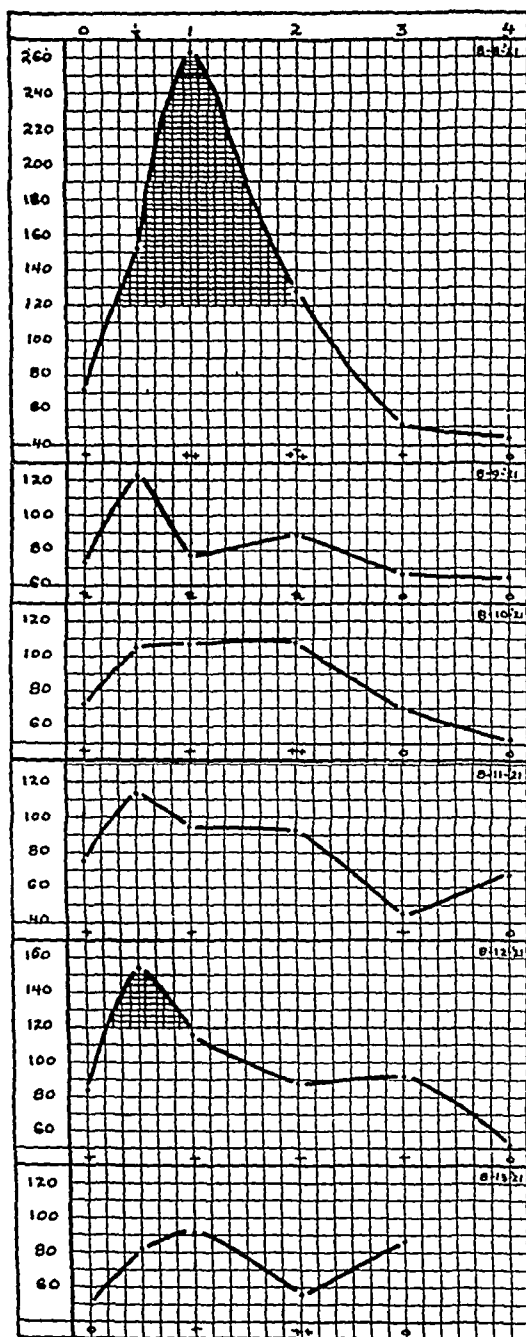


Figure XV. Charts showing the curves obtained in six glucose tolerance tests made on the author on six successive days. Note the progressive increase in the utilization of glucose.

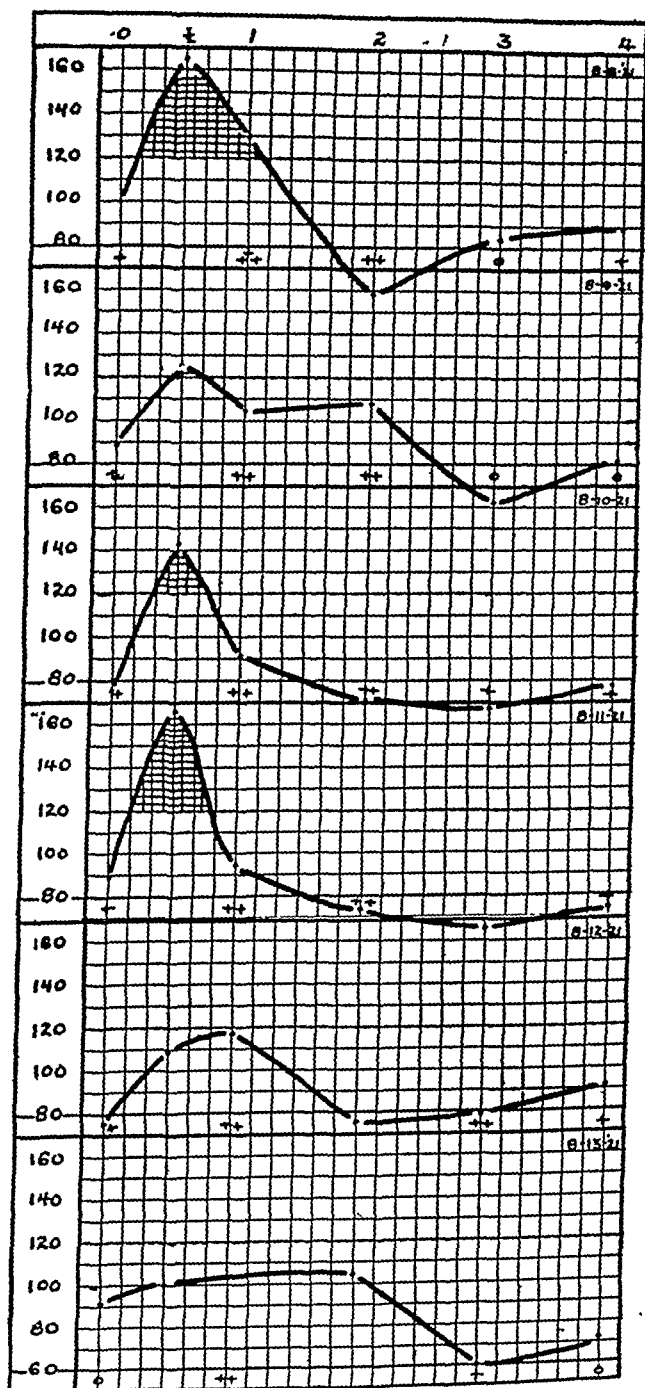


Figure XVI. Charts showing the curves obtained in six glucose tolerance tests made on the author's assistant (A. R.). Note the progressive increase in the utilization of glucose.

may be confronted. It has been shown that if a normal individual ingests abnormal amounts of carbohydrate daily for a period of time, the output of insulin will be quickened by this constant teasing, so that at the end of a week the response of the islands of Langerhans to the ingested glucose is more prompt than it was at the beginning.

In this connection I can cite an experimental study of which one of my assistants and I were the subjects. Daily glucose tolerance estimations for six successive days gave the results shown in Figures XV and XVI. It will be noted that the tolerance curve of each of us was lowered almost daily, so that at the end of the week each curve showed but a slight rise, an observation which indicates that the islands were responding more promptly to the stimulus of the ingested glucose than at the beginning of the experiment. We can assume that a similar condition exists in cases of hyperthyroidism in which the insulogenic apparatus is unimpaired. The metabolism of these patients is increased by the hyperthyroidism. As a rule, they eat voraciously, thus consuming a large number of calories; they have a special craving for sweets. The increased carbohydrate intake calls daily for an increased output of insulin, and such an increased output takes place as long as the islands can well supply the demand. As the result of the increased output of insulin, increased oxidation takes place and more glucose is burned per unit of time. In some cases the insulogenic function can control this increased activity uninterruptedly, and the respiratory quotient is increased until the patient is operated upon or treated in some other manner, when the hyperthyroidism subsides and the carbohydrate metabolism shifts back to the normal rate. But there are other cases in which the insulogenic reserve is not sufficient; or the increased metabolic strain continues so long that the insulogenic apparatus breaks down to a greater or less degree under the added strain—and there results first a slight disturbance of the carbohydrate metabolism which, if not relieved, becomes more marked until eventually a frank case of diabetes develops. The first step in this process, therefore, is the increased rate of function which, in some cases, goes on to the second stage and, in some, on still further until complete exhaustion of the islands occurs, just as any other organ

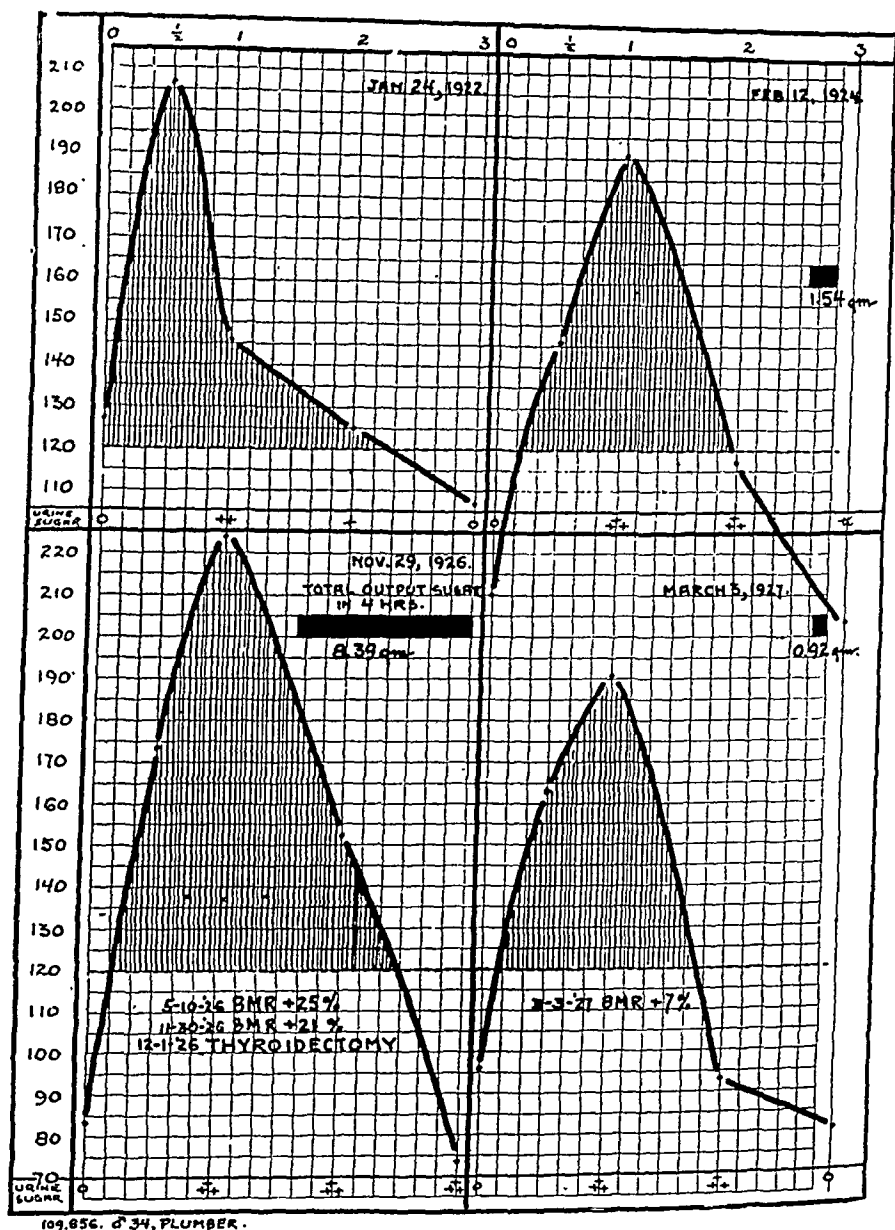


Figure XVII. Charts showing the findings in four glucose tolerance tests made in a case of hyperthyroidism (Case II). The first two curves were obtained when the patient's condition was normal, the third after the development of hyperthyroidism, the fourth after thyroidectomy had been performed.

of the body may become exhausted as the result of continuous hyperfunction.

This point is emphasized further by the fact that if we remove the thyroid gland in a patient in whom the carbohydrate tolerance has been decreased through the influence of hyperthyroidism, so that a mild type of diabetes has developed, the carbohydrate tolerance is improved (see Figure XVII). It would be interesting if we could have data regarding the condition of the islands of Langerhans during these successive stages in order that we might have *prima facie* evidence whether or not in these early stages the hydropic degeneration of the beta cells is demonstrable. But as patients do not die in these early stages, such final evidence cannot be secured. It certainly seems, however, as though we had sufficient clinical evidence to conclude that in every case of diminished carbohydrate tolerance the insulogenic processes are identical.

The following case-history is offered as presenting corroborative evidence of this conception that the insulogenic function may be progressively weakened by hyperthyroidism and in part, at least, restored by the removal of the thyroid gland.

Case II (109856): The patient was a man 34 years of age. He had been married for 10 years and had two healthy children. There was nothing relevant in the family history. He had always been in good health and had had no previous diseases excepting influenza. When I first saw him on January 21, 1922, he stated that two years before he had been examined by his family physician who had made a diagnosis of diabetes and had prescribed a diabetic regimen. Since that time no blood sugar examinations had been made, but the patient had been examining his own urine and had occasionally found sugar. He had lost 12 pounds in weight. He did not have thirst or frequency of urination. He presented the appearance of a man in perfect health except for the evidence of anxiety about the diabetes.

I made a glucose tolerance test on January 24, 1922, which gave a normal curve (Figure XVII) and showed a low renal threshold. I prescribed a heavy diet, rich in carbohydrates, for two weeks, and asked him particularly to eat an abundance of sweets during this period, at the end of which the fasting blood sugar was only 87 mgm. per 100 cc. and he had no glycosuria.

Periodic blood sugar and urine examinations gave the following findings:

Date		Blood Sugar mgm. per 100 cc.	Urine Sugar
1922	1-24	128	negative
	2-24	104	
	5-24	111	
1924	11- 1	102	negative
	2-11	97	plus
	2-12	80	negative
1926	2-17	87	negative -
	3-22	78 (1 ½ hrs. p. c.)	
	6- 2	95 (5 hrs. p. c.)	2 plus
	11-29	83	negative
1927	3- 3	96	negative

Throughout this period the man had been working hard and his diet had been like that of any normal individual.

In 1926 the patient grew restless, was quite nervous and did not feel well. Someone told him that he had a goiter, which frightened him and he consulted several physicians. He was told by the first physician consulted that he had hyperthyroidism and should be operated upon at once. The second consultation was with another internist who was quite definite in his statement that his trouble was neurosis and not hyperthyroidism (the patient was a Jew) and that an operation was not indicated. At that time his basal metabolic rate was found to be plus 25 per cent. He next consulted a surgeon who also did not consider this to be a case of hyperthyroidism and advised against operation. He consulted another surgeon who said he had hyperthyroidism and should be operated upon.

With this story he came to me asking for advice. One surgeon and one internist advised operation, another surgeon and another internist advised against operation. I found the basal metabolic rate to be plus 21 per cent and referred the patient to the surgical division for operation, following which all his symptoms subsided and he is now back at work and in perfect health.

While the above data are interesting, the point of special interest is found in the following findings: I made four glucose tolerance tests in this case during five years (Fig. XVII). Of these, the first two demonstrated that no diabetic condition was present. In 1926 hyperthyroidism developed and the blood sugar, though it returned to the normal level in less than three hours, nevertheless indicated a diminished insulogenic function. That is, as is shown by the height and length of the curve, the blood was flooded with sugar for two and a half hours and

sugar was excreted through the urine. This indicated that the carbohydrate tolerance had become diminished, or in other words, that the insulogenic function had begun to lag. According to our conception, the man was on the way toward diabetes unless the strain should be lifted. It was a comparison of this curve with the two that preceded it which made me decide that an operation was indicated, as I felt that by the removal of the thyroid gland we might be able either to restore the insulogenic function to its former status or at least to prevent further damage. Did we accomplish this? Note the curve made March 3, 1927, as shown in Figure XVII, which was made three months after the thyroidectomy! This demonstrates a definite improvement in the patient's carbohydrate tolerance, a return to the normal.

These curves appear to demonstrate (1) that hyperthyroidism exerts a destructive influence on the insulogenic function and (2) that the insulogenic function may be restored to normal or its further damage prevented by the removal of the thyroid gland.

That one cannot afford to disregard the presence of even slight glycosuria or of a slight degree of fasting hyperglycemia in patients with hyperthyroidism is well illustrated by the following case. Many patients of this type have fully developed diabetes which would go on unrecognized if one were looking for the classical picture of that disorder. The classical symptoms of diabetes are present only in well advanced cases, or in cases in which the onset is acute; the early cases, and those in which the onset is gradual, show few or no signs of the disease.

Case III (176410): The patient was a married woman 59 years of age. There was no familial history of diabetes or of thyroid disease. The patient had had measles, mumps, chicken pox, scarlet fever, whooping cough, tonsillitis and influenza. She had had two pregnancies and had one child living and well, the other having died soon after birth. When I first saw her on December 1, 1926, she complained of rapid heart, nervousness, loss of weight and goiter. Three years before, in 1923, she had had hyperthyroidism which had been treated by eight injections of boiling water into the gland, after which the symptoms had disappeared and she had been in good health until about May, 1926. Since the latter date she had been feeling very tired, the heart action had become rapid, she did not sleep well and never felt rested. Her appetite was poor, she had "gas on the

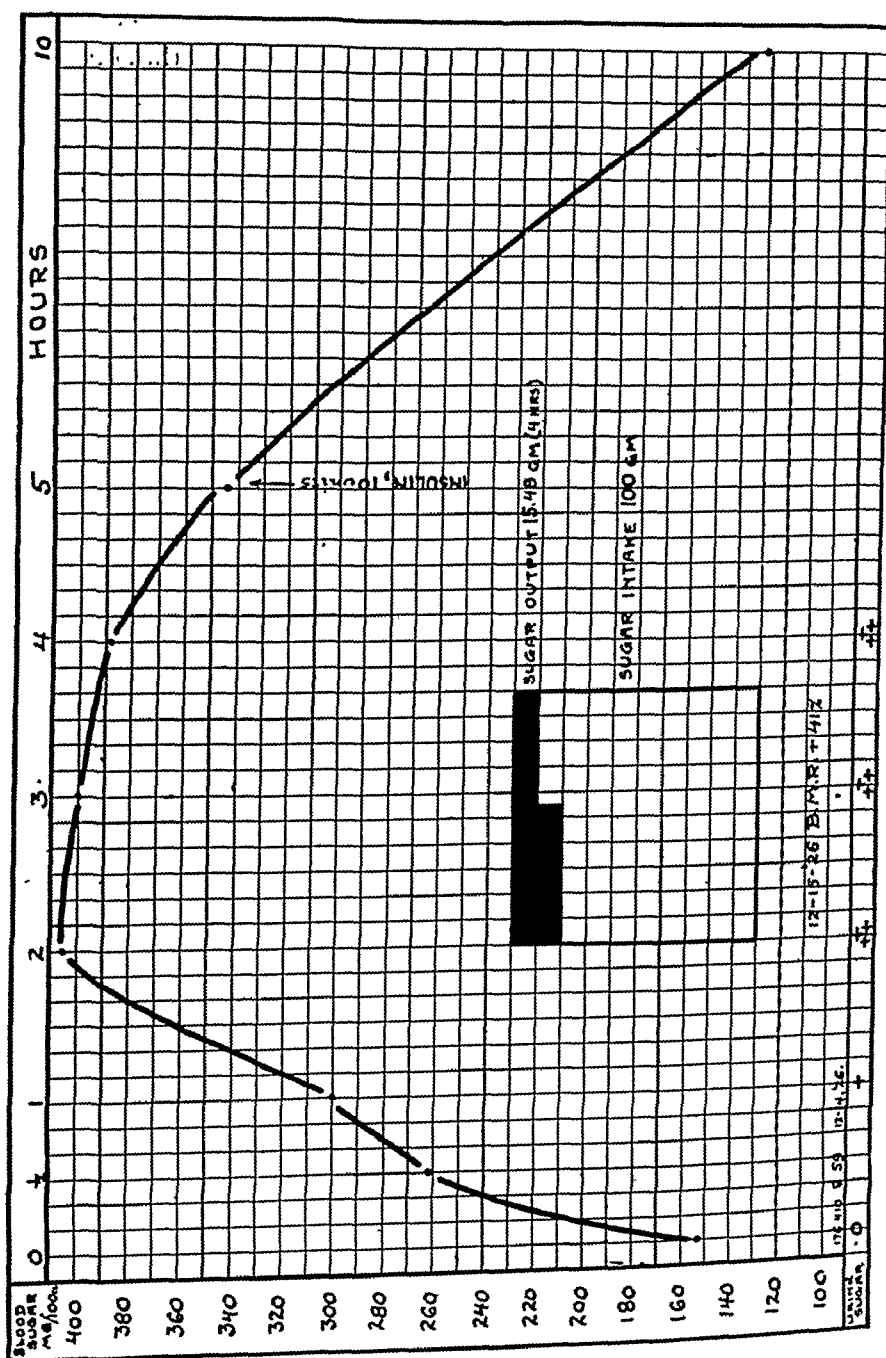


Figure XVIII Chart showing the findings in a glucose tolerance test at the time when this test was made. (Case 111). Although traces of sugar had been found in the urine previous to our examination, there was no fasting glycosuria and only a slight fasting hyperglycemia tolerance test made before operation in a case of hyper-

stomach" and was constipated. During the preceding four months she had lost 36 pounds and was considerably underweight. She had been in bed at various times during the preceding 10 or 12 weeks. She complained also of pain in the precordium radiating to the left arm. Physical examination and laboratory examinations gave the following pertinent findings: A definite adenoma with hyperthyroidism; glycosuria; blood sugar on three consecutive mornings—respectively 169, 172 and 153 mgm. per 100 cc., 3 hours p.c.; pulse rate, 88; blood pressure, 150/70; basal metabolic rate, plus 41 per cent.

This was obviously a second attack of hyperthyroidism in a woman past the menopause. As compared with the elevated basal metabolism, the moderate glycosuria and slight increase in the fasting blood sugar would seem of little importance, but nevertheless I made a glucose tolerance test on December 14, 1926, the results of which are shown in Figure XVIII.

Although the fasting blood sugar was but 153 mgm. per 100 cc. and there were no glycosuria and no classical symptoms of diabetes, yet, as may be seen on the chart, the blood sugar rose to 405 mgm. per 100 cc. during the second and third hours of the test and was still at 344 mgm. per 100 cc. at the fifth hour, when ten units of insulin were given intravenously; and even with the aid of insulin, the blood sugar did not reach the normal level before the tenth hour.

A thyroidectomy was performed on December 16th, 1926. Urinary analyses of 24 hour specimens while the patient was in the hospital gave the following findings:

Date	Vol. cc.	Sp. grav.	Sugar	Acetone
December 1, 1926			4 plus	
4,		1030	4 plus	
8,		1030	4 plus	
12,	2150	1007	neg.	2 plus
13,	575—	1013	neg.	2 plus
16, (thyroidectomy)	1725	1005	neg.	
17,	1200	1010	trace	2 plus
18,	550—	1015	neg.	2 plus
20,	1550	1006	neg.	neg.
21,	1425	1008	neg.	2 plus
22,	950	1010	neg.	2 plus

During her stay in the hospital she was on a diet of carbohydrate 100 grams, protein 60 grams, fat 128 grams—a total of 1800 calories. The fasting blood sugar examination gave the following findings:

Date 1926	Fasting Blood Sugar mgm. per 100 cc.	Insulin dosage (in units)	
December 11	172		
12	159	10	
13	147	10	
14	153	10-10	
15		10-10	
16	133	10	B. M. R., plus 41 per cent
17	221	10-10-10	Thyroidectomy
18	158	10-10-10	
19	124	10-10-10	
20	84	10-10	
21	113	10	
22	114		
23	112		Discharged from the hospital.

Following the thyroidectomy and with the help of a little insulin, the blood sugar returned to a normal level, where it has remained even since the insulin has been discontinued.

The importance of fasting blood sugar tests in the presence of hyperthyroidism is well illustrated also by the following case:

Case IV (144,190): The patient was a young Jewish woman, 21 years of age, who was first seen by me on November 18, 1924. Her father had died of diabetic gangrene and one sister had diabetes. She was very nervous and irritable and had crying spells and palpitation of the heart on the slightest exertion. These symptoms had been increasing during the preceding two years. She had lost 20 pounds in weight; easily became fatigued; had had abnormal thirst and polyuria for a year. She formerly had eaten large quantities of sweets. She had been examined 6 months before in New York and no glycosuria had been found.

On examination I found that the patient presented a typical case of hyperthyroidism. Her basal^a metabolic rate was plus 31 per cent. Her blood sugar was 600 mgm. per 100 cc.; CO₂, 38.5; plasma acetone, 3 plus; glycosuria, 3.3 per cent. The Wassermann test was negative. Although we had no definite data regarding the onset of the diabetes, it was evident that the hyperthyroidism had existed for two years and undoubtedly had preceded the diabetes.

The basal metabolic studies in this case can be summed up as follows:

Date	B. M. R. %	Place
April, 1924.....	Plus 23	New York
November, 1924.....	Plus 31	Cleveland Clinic
December, 1924	Plus 30	New York
April, 1925.....	Plus 65	New York
April, 1925 (1 week later).....	Plus 45	New York

The patient went back and forth between New York and Cleveland and consequently I did not see her frequently. She took large

amounts of insulin (60 units A. M., 50 units P. M.), and I had the impression that she did not adhere closely to her diet. She was in several hospitals at various times, and at one time went into coma, but recovered and continued, so to speak, to "drift along." She was not operated upon, but in New York received x-ray treatments over the region of the thyroid gland. I saw her for a few minutes in 1926, at which time she seemed to be all right, much of her nervousness having disappeared.

On January 16, 1927, she had a miscarriage and was taken to a local hospital. On the following day coma developed and she died. At that time she had a high blood sugar (256 mgm.); white count, 36,000; blood culture negative. A postmortem blood culture was not made. The patient was quite edematous at the time of her death.

In this case the symptoms of hyperthyroidism had somewhat subsided, but whether this was due to the x-ray treatments or to the use of insulin is hard to say. The important point is that the accident of miscarriage supervening upon an uncontrolled, severe diabetic condition was sufficient to bring about the end.

Had thyroidectomy been performed in time in this case, would that have relieved the strain on the islands of Langerhans and saved the patient from the development of diabetes? And if the diabetes had been discovered at an earlier stage and a proper regimen established would the fatal outcome have been avoided? Since the status of the carbohydrate metabolism before the development of hyperthyroidism is not known in this case, it is impossible to tell the sequence of the diseases. Was the patient a prediabetic and thus a prey to any disturbance which would precipitate diabetes, the disturbance in this case being hyperthyroidism? Or was her carbohydrate metabolism normal and did the diabetes develop in spite of it, as the direct result of the hyperthyroidism? A study of this case shows how essential it is that we investigate the carbohydrate metabolism in a large series of normal individuals in order to determine whether a normal carbohydrate tolerance can be broken down, or whether it is only in the case of a diminished carbohydrate tolerance that the system gives way under a strain.

In 1926 Marsh (75) discussed the relation of glycosuria to thyroid disease. He states that glycosuria is encountered in about two per cent of the cases of hyperthyroidism; but believes that two types of glycosuria occur in these cases: (1) symptomatic glycosuria; (2) diabetic glycosuria. Marsh tried

to differentiate these two types by the estimation of the R.Q. rather than by glucose tolerance estimation, although he also employed the latter measure. If, following the administration of a large dose of glucose the R.Q. rises to 90, he considers such a case to be non-diabetic. In the first case in his second table he offers the following findings from a glucose tolerance test and R.Q. determinations in a case of exophthalmic goiter:

	Fasting	Periods after ingestion of glucose		
		1 hour	2 hours	3 hours
Blood sugar mgm. per 100 cc.....	136	370	270	214
R. Q.	0.71	0.75	0.90	

The case was that of a man 32 years of age, who for six weeks had had polyuria, polydipsia, nervousness, palpitation of the heart and weakness, and had lost 33 pounds in weight. He had exophthalmos, lid-lag, difficulty of ocular convergence, goiter with thrill and bruit, a systolic murmur over the entire precordium and a fine tremor of the extended fingers. The basal metabolic rate was plus 38 per cent; pulse rate, 92; blood pressure, 124/60. He was excreting 11 grams of sugar in 24 hours, and his blood sugar was 420 mgm. per 100 cc. Glycosuria disappeared while he was on hospital diet, and he left the hospital sugar-free, with a basal metabolic rate of minus eight per cent. Marsh interprets the hyperglycemia and glycosuria in this case as due to a defect in carbohydrate mobilization rather than to a defect in the carbohydrate combustion, as is the case in true diabetes. At the end of his article Marsh makes the following statement: "The symptomatic glycosuria of hyperthyroidism demands no special management. The patient may be given a liberal diet and the defect in his carbohydrate metabolism ignored." (Note that he uses the term—"defect in carbohydrate metabolism.") "Treatment is directed at his thyroid disease, and as the latter is controlled, the glycosuria may be expected to disappear. Diabetes, on the other hand, demands very careful management."

If we are to accept Marsh's conception, where are we to draw the line between diabetic and non-diabetic hyperglycemia and glycosuria? Are we to disregard such classical symptoms of diabetes as hyperglycemia, a blood sugar of 420 mgm. per 100 cc., and the excretion of 11 grams of sugar, because of the

recent development of the symptoms of diabetes, which indicates that the islands of Langerhans are only functionally impaired? If we were to follow this rule we should have to rule out all mild and functional cases of diabetes whether or not they are associated with other diseases. Such a consideration as that offered by Marsh would, I fear, only tend to throw the whole problem of the differential diagnosis of diabetes into complete chaos. Why does Marsh advocate the glucose tolerance test as a means of differentiating the thyroid glycosuria from diabetic glycosuria and then disregard his own figures? Should a blood sugar figure of 214 mgm. per 100 cc. at the end of the third hour of a glucose tolerance test be disregarded, just because the case is one of hyperthyroidism? In Marsh's second case, in addition to high blood sugar figures (210-460) there was also an impairment of the R.Q. Any functional diabetic will present this additional evidence if he is allowed to remain untreated for a long enough period, just as he will show diminished blood sugar and a better R.Q. if he receives prompt treatment.

If one makes blood sugar examinations in any series of cases of hyperthyroidism one often finds: (1) a mild degree of hyperglycemia in the fasting blood; and more frequently (2) that the blood sugar is above 120 mgm. per 100 cc., three or more hours after a meal. This second value is the deciding point in making a diagnosis of diabetes or of an early disturbance of carbohydrate metabolism, for if the insulogenic function is normal then hyperglycemia will not be present three hours after a meal. Diabetes associated with hyperthyroidism or due to hyperthyroidism does not differ from diabetes due to any other cause, it is diabetes, and if unrecognized or disregarded, it will probably become severe in time. On the other hand, if the tendency to hyperglycemia is recognized early and receives prompt treatment, then the primary diabetic tendency will often disappear completely. Because of the fact that the glycosuria or hyperglycemia, or both, which are associated with hyperthyroidism often disappear after thyroidectomy, many authors have not been willing to recognize this condition as diabetes, but prefer to regard it as merely a temporary functional disorder of carbohydrate metabolism, which disappears after the removal of the thyroid gland. Were we to accept this

point of view in regard to hyperthyroidism, then we should have to do the same in all other cases in which hyperglycemia and glycosuria, whatever their origin, disappear. In other words, we should have to disregard as cases of diabetes all those in which the hyperglycemia is functional in type.

"Functional diabetes," as manifested by what may prove to be a transient hyperglycemia, exists because the islands of Langerhans have been slightly damaged, i.e., have undergone the so-called hydropic degeneration which, as Copp and Barclay (76) have demonstrated, is still a reversible process. In such cases by simply removing the cause of the over-loading of the insulogenic function we can clear up the condition. Thus when the thyroid gland is the causative factor, then thyroidectomy may result in the restoration of the insulogenic function, that is, it will cure such cases of "functional diabetes" as are associated with hyperactivity of the thyroid gland. The effect of thyroidectomy, therefore, instead of proving that hyperthyroidism bears no etiological relation to diabetes, on the contrary, offers strong proof that it is a potent etiological factor.

Does Marsh believe that cases in which glycosuria is associated with thyroid disease should be disregarded? Is it not rather our duty to investigate and study this type of borderline case more closely—to observe them for a decade or two—before we make any final statement regarding them? Even though the etiology of the metabolic disorder may be somewhat different in cases of hyperthyroidism than in cases of uncomplicated diabetes, we do know that many of these cases in the former group become frankly diabetic later. Does diabetes develop because the carbohydrate metabolism was "different," or because the insulogenic supply has been steadily decreasing? *A steadily decreasing insulogenic supply is diabetes*, whether one recognizes it in its earliest stages or only after the islands of Langerhans have become exhausted and frank or total diabetes has developed.

Effect of Thyroidectomy on Carbohydrate Tolerance. We have already offered evidence that in a considerable percentage of cases, feeding with thyroid extract, as well as hyperthyroidism, increases the blood sugar content, and if carried far enough, in some cases induces a functional state of diabetes. One can

observe this in any group of clinical cases in which the lagging carbohydrate tolerance varies from a very slight degree to a severe stage of diabetes. In some of the latter cases the diabetes will have passed beyond the functional stage, so that the changes in the islands of Langerhans are no longer reversible, and the insulogenic apparatus will have become permanently damaged.

If artificially induced or clinical hyperthyroidism produces the above picture, then one naturally inquires whether or not the elimination of the thyroid in such cases will increase the carbohydrate tolerance.

Friedman and Gottesman (77) report some interesting experiments in thyroidectomy and ligations of the thyroid arteries which were performed in depancreatized dogs, the protocols of which I offer as follows:

DOG NO. 100—WEIGHT 14 KGM.

Date, 1921	Urine Sugar
Jan. 12 Partial pancreatectomy.....	2-3% to Jan. 19
19 Both inferior thyroid arteries ligated.....	Glycosuria continued until Jan. 26
26 Complete thyroidectomy (sparing parathyroids)	Negative
Feb. 5 Blood sugar, 95 mgm. per 100 cc.; 3.4 grams pancreatic tissue removed.....	Negative
9 Blood sugar, 86 mgm. per 100 cc.; 150 grams glucose by stomach tube.....	Negative
May 9 Blood sugar, 66 mgm. per 100 cc.; rest of the pancreas removed (10 grams).....	Negative
14 Wound opened—dog died. Autopsy showed complete absence of pancreas. Weight, 15.9 kg.	

DOG NO. 106—WEIGHT 7.52 KGM.

	Urine Sugar
Mar. 2 Complete pancreatectomy (18.2 grams)	
3	Plus (5-6%)
5 Superior and inferior thyroid arteries ligated	Present in decreasing amounts until March 8.
8	Negative until March 19, when distemper developed and dog died
2 Blood sugar, 76 mgm. per 100 cc.	
4 Blood sugar, 250 mgm. per 100 cc.	
5 Blood sugar, 192 mgm. per 100 cc.	
6 Blood sugar, 90 mgm. per 100 cc.	
7 Blood sugar, 50 mgm. per 100 cc.	

Autopsy revealed complete absence of pancreas.

Thus, according to the findings of these authors, in dogs the diabetes which results from complete pancreatectomy may be rendered less severe by ligation of all the vessels of the thyroid gland and glycosuria can be caused to disappear by the subsequent thyroidectomy.

Janney and Isaacson (20) studied the effect of thyroidectomy on the carbohydrate tolerance of dogs by means of glucose tolerance curves. Some of their results are given in Figure XIX. The significant point demonstrated by these curves is that even though each was normal before thyroidectomy, after thyroidectomy the glucose tolerance was still further increased, a fact which suggests that the thyroid gland exerts an inhibitory action on the insulogenic function.

Holman (78) published a report of three cases of hyperthyroidism in which operations had been performed. This report is of special interest because during a very severe and alarming attack of postoperative hyperthyroidism in one of the patients the blood sugar was found to be 48 mgm. per 100 cc. This patient responded well to the administration of glucose. The other two patients did not have a severe reaction to the operation, and both showed a rise of blood sugar with the subsequent return to a slightly subnormal level 24 hours later.

Lund and Richardson (10) studied the blood sugar after operations on the thyroid gland in an attempt to discover whether or not hypoglycemia developed after the operation. Nitrous oxid-oxygen anesthesia was used, the duration of the operations being from 15 minutes to one hour. They found a rise in blood sugar in all operations on the thyroid gland in cases of hyperthyroidism similar to that in all other cases. They did not find hypoglycemia in any case.

My observations of the effects on the blood sugar of various operations are summarized in Table X and Figure XX.

Rohdenburg (3) reports the case of a boy 18 years of age in whom hyperthyroidism developed as a result of the administration of thyroid extract. The patient was kept in bed for four months without any improvement. A partial thyroidectomy was therefore performed, and six months later the urine was sugar-free, even after the ingestion of large amounts of carbohydrate.

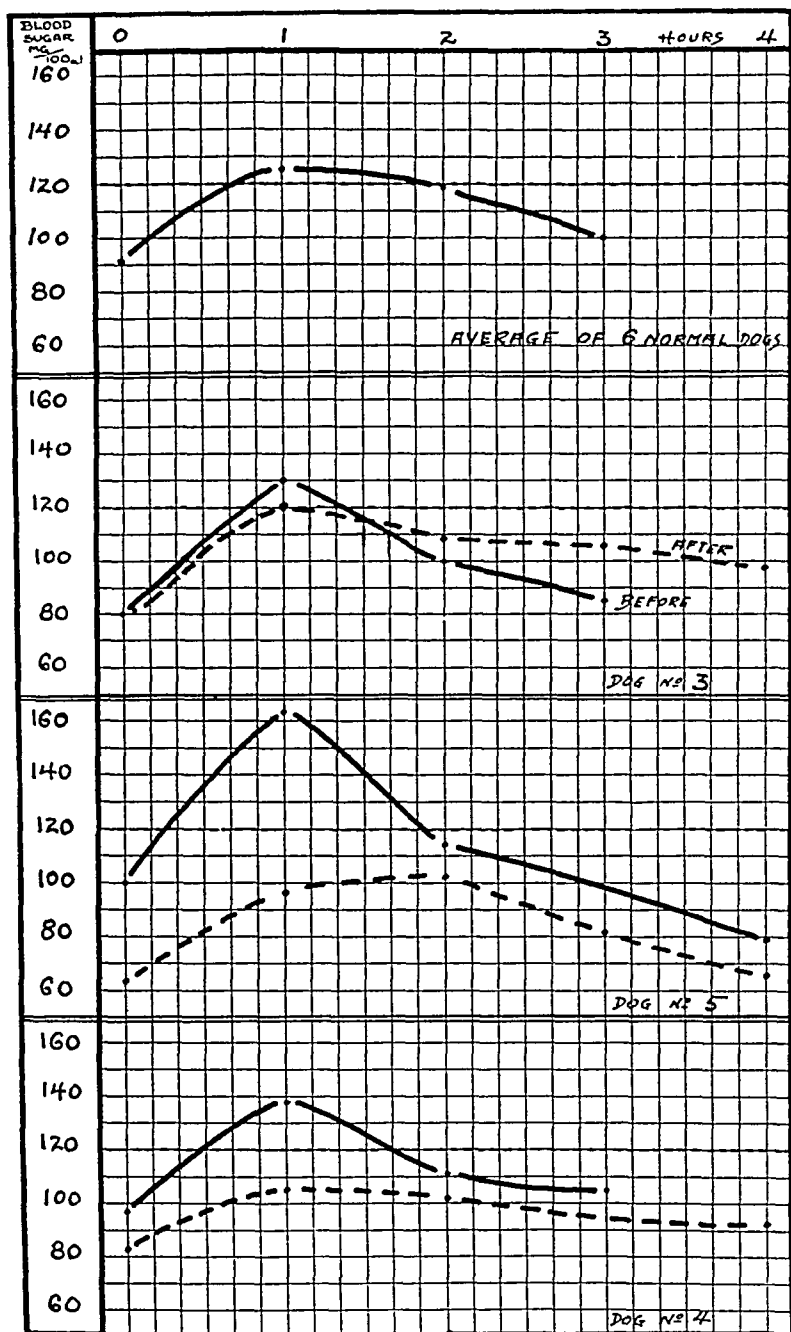


Figure XIX. Charts showing curves plotted from the findings of Janney and Isaacson in their investigations of the carbohydrate tolerance of dogs before and after thyroidectomy. In the first chart is given the average curve of six normal dogs; in the second, third and fourth, the curves in the case of individual dogs before thyroidectomy (the heavy line) and after thyroidectomy (the broken line).

Rohdenburg reports also the case of a woman, 53 years of age, in whom a partial thyroidectomy had been performed for exophthalmic goiter. Several years later glycosuria developed; more of the thyroid gland was removed and the glycosuria disappeared. (Figure XXI.)

On the other hand, Fitz (51) states that partial thyroidectomy has no curative effect on diabetes.

TABLE X

THE EFFECT OF OPERATIONS PERFORMED UNDER GENERAL ANESTHETICS
ON BLOOD SUGAR

Operation	Blood Sugar Before Operation	Blood Sugar After Operation	Percent of Increase	Percent of Decrease
Massive resection for carcinoma of pancreas, colon, stomach.....	182	395	117
Gall bladder drainage.....	131	143	9
Lobectomy.....	78	147	89
Thyroidectomy.....	88	98	11
Thyroidectomy.....	84	109	29
Thyroidectomy.....	106	118	11
Thyroidectomy.....	133	168	26
Thyroidectomy.....	155	193	27
Thyroidectomy.....	76	89	17
Tonsillectomy.....	303	434	43
Tonsillectomy.....	95	89	6
Hemorrhoidectomy.....	97	68	42
Incision of infected thumb.....	150	139	7

In my own series I need only to call attention to the following cases:

Case No.	Sex	Age	Before Thyroidectomy	After Thyroidectomy	Glucose Tolerance
			B. M. R. plus %	B. M. R. plus %	
109,856.....	M	34	21	7	improved
164,227.....	F	28	25	12	improved
160,342.....	F	60	41	..	improved
178,992.....	F	39	81	6	slightly worse

Thus of four cases in which I had the opportunity to recheck the glucose tolerance after thyroidectomy, marked improvement was shown in three and in one there was a slight retrogression. In the last case, however, a period of less than two months has passed since the operation, so that the result cannot yet be considered to be conclusive. The history in this final case is as follows:

Case V (178,992): A woman, 39 years of age, was first seen on February 8, 1927. She had lost 50 pounds in weight in less than a year. For seven months she had been very nervous, had had a rapid heart, had perspired and had noted an increasing lack of energy and increasing irritability. She had had an enlargement of the thyroid

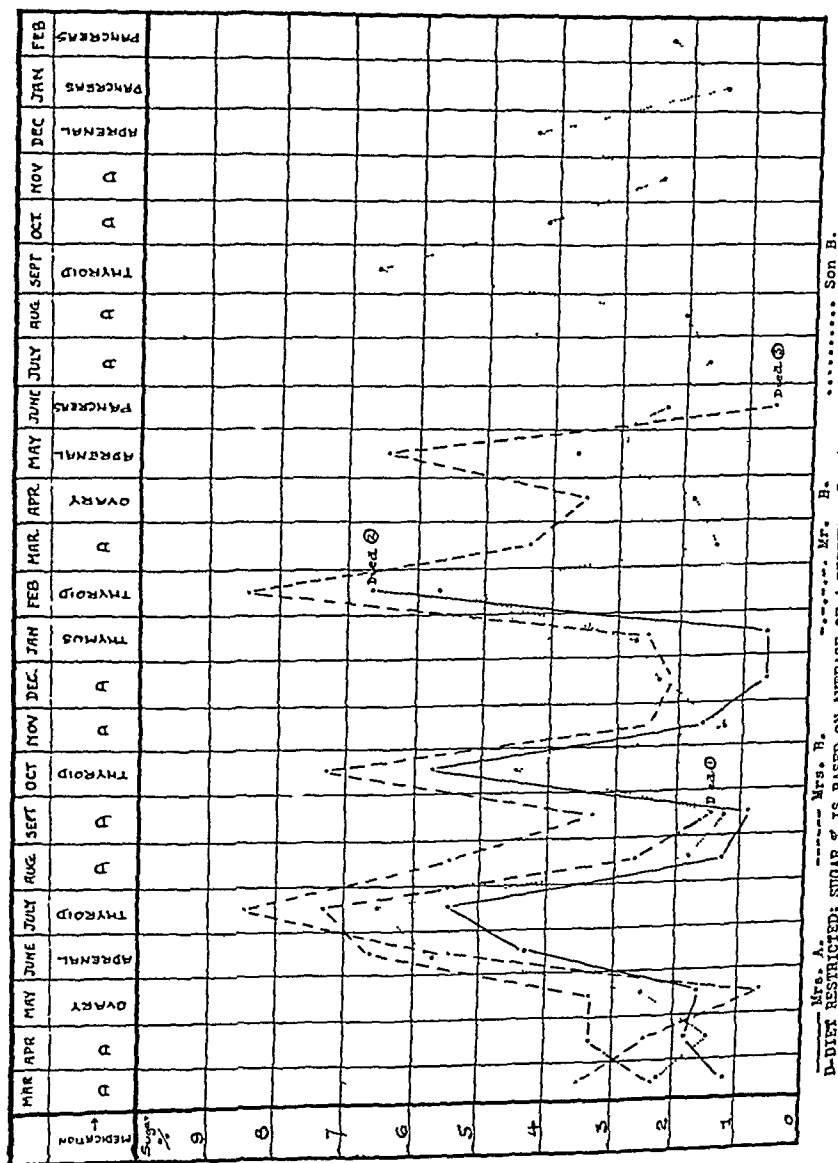


Figure XXI Chart showing the effect of adm insulin of thyroid gland substance upon glyco-emia in four cases (After Rolstenburg)

gland for 15 years. Nearly a year before she had had an attack of influenza and had not been well since that time. When I first saw her, her weight was about normal, but a year before she had been very much overweight (52 per cent). Her pulse rate was 144, blood pressure, 185/48. The fasting blood sugar was 161 mgm. per cc., and she had glycosuria—1.7 per cent. The basal metabolic rate was plus 81 per cent. Two glucose tolerance tests, one made before and one two months after thyroidectomy, have already been shown in Figure IX. During her stay in the hospital the fasting blood sugar was consistently normal and she received no insulin. It may be noted from this chart that while the second tolerance test showed a somewhat more prolonged hyperglycemia than that shown in the first test, yet the sugar output in the second test is much less than in the first, viz., only 0.15 gram, as compared with 5.46 grams. One wonders whether the renal threshold has changed or whether the permeability of the renal filter increased during the active stage of hyperthyroidism. The tests are but two months apart. Clinically the patient is well.

The Effect of Anesthesia on Blood Sugar. The effects of surgical operations on the blood sugar have been studied by Dewes (79) and by Epstein and Aschner (80). They found that hyperglycemia was produced by surgical anesthesia if the procedure was serious or prolonged. Epstein and Aschner found no change in the blood sugar in four minor operations done under local anesthesia. Five cases in which nitrous oxid-oxygen anesthesia was used showed an increase of blood sugar of from 10 to 30 mgm. per 100 cc. In sixty cases in which ether anesthesia was used there was a marked rise in the blood sugar—of over 100 mgm. per 100 cc., in some cases; a slighter rise was shown in some cases; and none at all in only three.

Insulin Treatment of Hyperthyroidism. During the past two or three years reports regarding the treatment of hyperthyroidism with insulin have appeared in the literature. With the advent of insulin it seemed logical to use it in the treatment of those cases of hyperthyroidism in which glycosuria and hyperglycemia were present. Much to the surprise of many of these reporters, however, in some cases not only were the symptoms of diabetes improved but the hyperthyroidism itself was either lessened in degree or even disappeared.

Thus Charvat (81) describes the case of a woman, 25 years of age, who had experienced a sudden onset of severe hyperthyroidism in 1921, the basal metabolic rate at that time being

plus 26 per cent. In 1925 the classical symptoms of diabetes appeared—glycosuria, 6 per cent and blood sugar, 340 mgm. per 100 cc. A glucose tolerance test with 50 grams of glucose gave the following findings:

	Fasting	Periods after ingestion of glucose ½ hour	1 hour	2 hours
Blood sugar.....	340	450	490	450
Mgm. per 100 cc.				

The patient excreted from 40 to 60 grams of sugar in 24 hours. For four months she was on a reduced diet and received insulin twice a day, without much effect on the symptoms of

TABLE XI
RESULTS OF TREATMENT OF HYPERTHYROIDISM WITH INSULIN

Author	Number of Cases	Improved	Worse	No Change
Castex. .	18	4	3	11
Charvat. .	1			
Charvat	5	3		2
Charvat ..	5	5		
John..	2	1		1
Lawrence	4	3		1
Merklen ..	1	1		
Puchulu .	1			
Senga .	3	3		
Thomson .	1	1		

diabetes, excepting that she excreted less than ten grams of sugar daily and the acetone in the urine disappeared, although the glycemia remained at about 300 mgm. per 100 cc. While the insulin seemed to have no effect on the diabetes, the hyperthyroidism improved markedly; the exophthalmos almost completely disappeared; the patient became quiet, slept well, and gained 8 kgm. in weight in ten weeks, the tremor of the fingers disappeared, and even the goiter became smaller by 2.5 cm. In the third month of this treatment the goiter had decreased still more; the basal metabolic rate was only plus eight per cent, the pulse rate 80, and all symptoms of hyperthyroidism had disappeared. Although the hyperthyroidism was cured, in February, 1926, the patient went into diabetic coma and died. Charvat thinks that insulin has some direct action—either primary or secondary—on the thyroid aside from its influence on the carbohydrate tolerance.

In 1925 Charvat (82) reported five cases of hyperthyroidism which had been treated with insulin. In two of these the

basal metabolic rates were plus 45 and plus 30 per cent, respectively. One of these patients left the clinic early, so that only a slight improvement was observed. The other patient remained for four weeks, during which time she gained seven kgm. in weight; the pulse rate was reduced from 100 to 76; the exophthalmos decreased; and although there was no change in the size of the gland, subjectively the patient felt well. In the case of another patient who had had a postoperative recurrence of hyperthyroidism, after ten days of treatment with insulin the pulse rate was reduced from 160 to 80; it then increased again to 100, where it remained. There was no change in weight, but the symptoms were markedly relieved. In another case in which hyperthyroidism had been induced by the use of iodine, treatment with insulin for four days produced no effect. In the fifth case the pulse rate fell from 110 to 90 within a few days and subjectively the patient felt well.

In this publication Charvat makes the following statement:

"If we summarize our results, we can say that we have obtained splendid results in several cases, but our desire to find in insulin a specific anti-Basedowian medicament was not fulfilled. In all cases we were able to restore, at least partly, the patient's condition, as was evidenced by a more or less marked increase in weight; but at the same time, in all the cases which we observed we had the impression that primarily the insulin did not directly affect the function of the thyroid itself, but rather the metabolism of the peripheral cells, into which the insulin penetrated as a nonspecific energy-sparer and fat depositor." In other words, "we felt that the patients who were emaciated and were standing their Basedowian disease poorly were transformed into fatter, more comfortable Basedowians, who were, however, in substance, still Basedowians."

Puchulu (83) mentions the favorable effects of insulin in cases of hyperthyroidism.

Senga (84) reports three cases of hyperthyroidism in which insulin was employed with good results, the basal rate having been diminished, the body weight increased, and the general nervous condition and the tremor having subsided, though the gland had diminished but slightly in size.

Castex *et al.* (85) used insulin—20 units daily for from 10 to 20 days—in the treatment of 18 patients: (1) with exophthalmic goiter; (2) with simple goiter associated with the meno-

pause, these cases showing symptoms of hyperthyroidism; and (3) with thyroid insufficiency. In three of these cases the basal metabolic rate was increased, in three it was lowered, in one instance it was lowered to normal.

Lawrence (86) tried to eliminate all extraneous influences in four cases of well advanced hyperthyroidism, and did not begin to use insulin until mental and bodily calm was established. The first case was that of a woman, 23 years of age, in whom the hyperthyroidism was so severe that the surgeon considered that operation was contraindicated. The patient was kept quiet for seven weeks, without insulin, but her condition became worse, and she was losing weight. During this time she received sterile injections of water. Injections of insulin were then started without the patient's knowledge. Four days later she announced that her neck felt easier; after ten weeks, during which she received 80 units of insulin daily, she had gained 34 pounds, the thyroid had become reduced in size, her pulse rate had fallen from 114 to 78, and the basal rate from plus 58 per cent to plus 13 per cent. She was discharged from the hospital apparently well. The second case reported by Lawrence was also that of a woman, 28 years of age. In eight weeks she gained 24 pounds and was discharged practically well. The third patient, a woman, 50 years of age, who had an adenoma of the thyroid, reacted to the treatment with insulin only by a slight increase in weight. The fourth case was that of a woman, 47 years of age, with a nodular struma. This patient did not react to the insulin.

Merklen *et al.* (87) report the case of a woman with a typical exophthalmic goiter, whose first attack of hyperthyroidism developed post-partum. Her condition improved after the use of hematothyroidin. A second attack of hyperthyroidism was followed by diabetes, as shown by glycosuria and a blood sugar level of 280 mgm. per 100 cc. Insulin was given in doses of 20 units per day; both the diabetes and the hyperthyroidism improved.

Thomson (88) reports the case of a middle-aged woman who, three weeks after the onset of exophthalmic goiter, was almost maniacal. She vomited constantly for four days, had a pulse rate of 150, and had auricular fibrillation. The condition seemed desperate, and after two days all other treatment

was stopped and the administration of insulin was started with doses of five units each, three times a day, together with frequent sweetened drinks. There was no glycosuria, but the mouth of the patient was parched, and she complained of thirst. Within a few hours definite improvement was noted, and this continued. The dose of insulin was increased to 30 units daily, in three doses of 5, 20, and 5 units, respectively. Hypoglycemia developed and the insulin was changed to two daily doses of 5 units each. The vomiting stopped, abdominal distress disappeared, and mentally the patient became more calm. These results are the more remarkable since the patient was apparently in a dying condition when she was brought to the hospital.

Bodansky (89) and Ducheneau (90) found that thyroidectomy enhanced the activity of insulin. Burn and Marks (91) showed that thyroidectomized rabbits were three to nine times more sensitive to insulin after the operation than before.

My own experience with the use of insulin in cases of hyperthyroidism is unlike that of the authors cited above. All cases in which the carbohydrate metabolism is slightly disturbed respond promptly to insulin, as one would expect. Small doses of insulin in addition to a regulated diet, together with the administration of iodine and rest in bed, do greatly improve the condition of these patients. The body is thus given an opportunity to store glycogen in the liver, which is a cardinal principle in the treatment of all cases of hyperthyroidism, whether they are diabetic or non-diabetic. In one severe case in which diabetes had followed the onset of hyperthyroidism in a young man, whose basal metabolic rate was plus 89 per cent, the patient did not respond in any way to insulin as far as the hyperthyroidism was concerned, and even after a double lobectomy his basal rate continued to be as high as plus 71 per cent. In this case a small nodule of thyroid tissue, one by two cm. in size, had been left; after this was removed, the basal metabolic rate became normal, and the myocarditis and diabetic condition were improved.

One patient, however, was distinctly benefited by the use of insulin and all the symptoms of hyperthyroidism subsided, so that it has not been necessary to operate. From a condition of serious invalidism this patient has progressed so that at the present time she is leading an active life. Insulin has been

discontinued now for nearly a year, and her blood sugar is remaining normal on a fairly liberal diet. This case seems of sufficient interest to justify the following detailed report:

Case VI (167,806): The patient was a married woman, 61 years of age. The family history contained no pertinent information. The patient had had mumps and whooping cough in childhood; measles and pneumonia at the age of 18 years; tonsillitis, rheumatism, and pleurisy later in life; typhoid fever at the age of 40. There was no history of jaundice or of gall-bladder disease. An ovarian tumor had been removed in 1907 and a herniotomy had been performed in 1910. The patient had three living and healthy children.

Diabetes had been definitely discovered a few days before I first saw her, on June 5, 1926, although she had had the classical symptoms for several months. She weighed 147 pounds, but her usual previous weight had been 187 pounds (the normal weight for her height, 5 feet 4 inches, would be 131 pounds). Two weeks before she had had a vomiting spell which lasted for four hours. She said that a diagnosis of gastric ulcer had been made several years before, and during the preceding five years she had had four or five hemorrhages from the stomach. She had recently had dimness of vision. She had nocturia, being obliged to urinate twice each night.

Physical examination showed a well nourished woman with no pallor. Her blood pressure was 140/76. The pupils were equal, reacting well to light and accommodation. The ears were normal. There was no adenopathy. A moderate sized adenoma of the thyroid was present. The lungs were clear. The heart was not enlarged; the rate was 90; regular, no murmurs or irregularity were detected. The abdominal wall was lax. She had a ventral hernia. The spleen was greatly enlarged, firm and smooth, extending about six inches below the costal margin. There was no enlargement of the liver.

The Wassermann test was negative. The blood clotting time was five minutes. There were no bile pigments in the plasma. The serum bilirubin was 0.6 mgm. per 100 cc. There were 170,000 blood platelets per cu. mm. The blood clot retracted in 1½ minutes. The blood sugar was 352 mgm. per 100 cc. Urine sugar was one plus. There was no albumin. X-ray examination of the gastro-intestinal tract gave normal findings.

The diagnosis was: Diabetes mellitus, Banti's disease, hyperthyroidism and ventral hernia.

Insulin and a diabetic regimen were prescribed and on August 16, 1926, a little more than two months later, the condition of the patient had improved greatly. The nervousness which the hyperthyroidism was causing had practically entirely disappeared, she looked well and said that she felt well. At that time she was taking ten units of insulin per day and the diabetic condition was evidently under control. There was no change in the size of the spleen, which

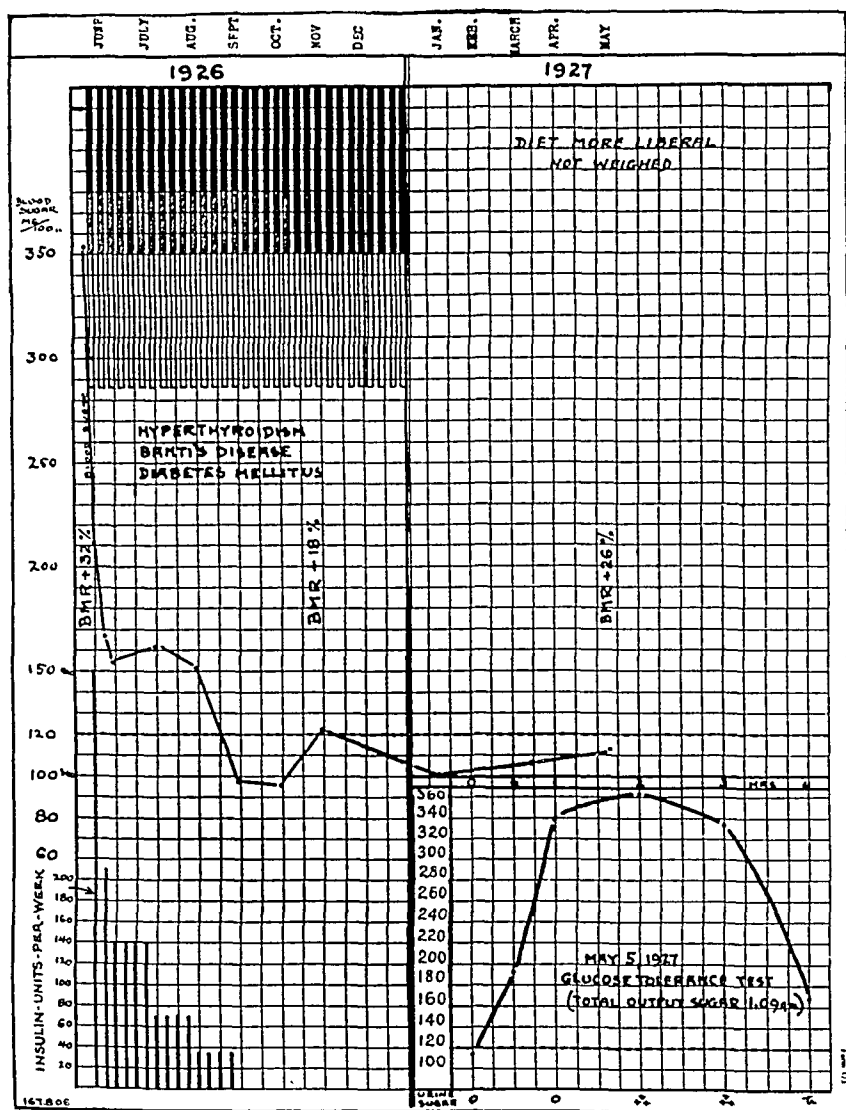


Figure XXII. Chart showing the course of a patient with hyperthyroidism, diabetes and Banti's disease, who was under treatment with insulin (Case VI).

could easily be felt from four to five inches below the costal margin.

One month later, on September 16, 1926, the patient was feeling "fine," was working, attending social functions and still steadily improving. Her general condition was normal excepting for the sensation of pressure in the abdomen from the enlarged spleen.

Figure XXII is a graphic representation of the data in this case. It will be seen from this that the patient's fasting blood sugar remained normal and she remained sugar-free until May, 1927, on a fairly liberal diet, which was only estimated, not weighed. Except for exophthalmos, which had not receded, she had no symptoms of hyperthyroidism, and it looked as though the diabetic condition might also have subsided. In order to test the latter condition a glucose tolerance test was made on May 5, the results of which are shown in the lower right corner of Figure XXI. The curve indicates definitely a diabetic condition, showing that the diabetes is controlled but not eliminated. A basal metabolism estimation was also made, and this showed a rate of plus 26 per cent. Clinically, therefore, this patient is well, but from a laboratory standpoint she is still a diabetic with a high basal metabolic rate.

Postoperative Acidosis. Acidosis is a well recognized postoperative complication of thyroidectomy. The pulse rate in such cases is high and the patient becomes semicomatose or stuporous immediately after operation. Is the acidosis in these cases of the same type as diabetic acidosis? Diabetic acidosis is due to the inability of the organism to burn glucose, this in turn producing an incomplete combustion of fats with the resultant accumulation of ketone bodies in the blood stream (acetone-diacetic acid-beta oxybutyric acid) and consequent acidosis. In uncomplicated hyperthyroidism, however, there is no such inability to burn glucose, but there is rather an inability to store glycogen and a general increase of the metabolic processes, so that all available carbohydrate, including the glycogen reserve of the liver and muscles is utilized, with resultant *hypoglycemia*. Holman (84) cites a case of hyperthyroidism in which the basal metabolic rate was plus 29 and plus 35 per cent. After thyroidectomy, the pulse rate rose to between 180 and 250, immediately after operation, this very high rate lasting for 60 hours. Twenty-four hours after the operation the patient was in a semicomatose condition and her blood sugar at that time was found to be only 48 mgm. per 100 cc. Glucose solution—20 per cent—was administered, and immediately she became conscious, but six hours later she again went into a deep stupor. She was

again given glucose, and again immediately became conscious. It is clear that in this case the stupor was due to hypoglycemia, a condition similar to the hypoglycemia of an insulin reaction.

SUMMARY

A report is offered of a study of the carbohydrate metabolism in 92 personal cases, together with a discussion of the pertinent literature. The following conclusions are reached:

1. There is no glucose tolerance curve specific for hyperthyroidism. That is, a definitely diabetic type of curve may be present in a mild case of hyperthyroidism and a normal curve may be present in a very severe case of hyperthyroidism. While hyperthyroidism, like infection, obesity, overeating, etc., may make manifest the presence of a latent form of diabetes or may change this prediabetic condition into true diabetes, I believe that hyperthyroidism rarely induces a diabetic status in an individual in whom there is a normal insulogenic reserve. The change from a prediabetic to a diabetic status, which is sometimes associated with hyperthyroidism, I believe to be the result of the overeating, which, in turn, is due to the increased metabolism. The food which is usually craved and eaten by these patients is especially rich in carbohydrate, and thus an unusually heavy load is thrown on the islands of Langerhans. If this over-load continues over a long period of time it is logical to expect that the islands will become exhausted, with a resultant breaking down of the carbohydrate metabolism; the classical picture of diabetes will then be superimposed upon that of active hyperthyroidism.

2. Thyroidectomy lowers the total metabolism and in consequence improves the carbohydrate tolerance. In cases in which little or no improvement follows thyroidectomy this is due to the fact that lack of proper diabetic treatment or insufficient treatment has followed the operation.

3. If diabetes develops after a thyroidectomy, this is due either to other extraneous factors such as produce diabetes in other cases or to the fact that an insufficient amount of thyroid tissue has been removed. In the latter case, when more of the gland is removed, the diabetes is improved.

4. A number of authors, with whom I agree, believe that hyperthyroidism plays a fundamental etiologic rôle in the dis-

turbances of endocrine equilibrium which constitute the diabetic syndrome.

5. Glycosuria and hyperglycemia (either fasting or, more often, two and one-half hours after a meal) are not uncommonly present in hyperthyroidism. When found they should not be disregarded, but their significance and their relationship to the carbohydrate metabolism should be determined by appropriate tests.

6. I consider that the presence of hyperglycemia two and one-half or more hours after a meal is an expression of an insufficient insulogenic function. While I appreciate that other physiological factors are concerned, I consider that these are of secondary significance; and whatever academic interest they may have, they should not be allowed to interfere with the institution of the appropriate measures for the safety of the patient.

7. The intervention of the menopause in a case of hyperthyroidism may cause hypertrophy of the islands of Langerhans with the resultant cure of a coincident diabetes. This probably, however, is a rare occurrence, for but few cases are reported in the literature.

8. The glycogen depletion of hyperthyroidism increases the tendency to acidosis. This factor is aggravated in cases in which diabetes is present. The ingestion or the intravenous administration of glucose before or after operation, with or without insulin, according to the indication in the individual case, would seem to be a logical procedure. The factors which influence the glycogen depletion are probably the following:

(a) Toxic influences which directly affect the parenchyma of the liver cells.

(b) A high metabolic rate which causes increased consumption of carbohydrate and depletes the insulogenic stores, which in turn depletes the glycogen store in the liver. Such a depletion is also shown in uncomplicated cases of hyperthyroidism which do not show a high blood sugar.

9. Patients with hyperthyroidism in whom a frank diabetic condition of severe type is not present, but merely a mild degree of disturbance of the carbohydrate metabolism, I consider to be "functional" diabetics. Up to a certain point diabetes is a reversible process. These functional cases clear up

eventually after thyroidectomy or some other type of treatment, but without such treatment they do not clear up and frank diabetes develops unless the prediabetic or functional condition be extremely mild. For that reason I have emphasized the importance of taking cognizance of a delayed glucose tolerance curve in cases of hyperthyroidism. Some authors consider this hyperglycemic condition to be due to an over-production of sugar in hyperthyroidism, and offer as an explanation for this view the normal rise of the R. Q. curve after the ingestion of glucose. This is quite true up to a certain point. The increased demand for insulin is satisfied as long as the supply can cope with the demand. But when the supply of insulin is exhausted, even the R. Q. comes down to a diabetic level. For this reason the pancreas should be protected whenever a weakening of the carbohydrate metabolism is evident. Interesting as it may be scientifically, it is of little immediate consequence to determine *why* the liver of a patient with hyperthyroidism is glycogen-free or glycogen-poor. The important fact is that it is glycogen-free or glycogen-poor, and the medical problem is to restore the normal status of the liver.

10. The administration of thyroid preparations is not without danger. It may precipitate hyperthyroidism, and may even produce diabetes.

11. In my series of 100 glucose tolerance tests in 82 cases of hyperthyroidism and 10 cases of colloid goiter, fasting glycosuria was present in 19 cases and absent in 81 cases. Sixty-six per cent of the curves indicate an impaired tolerance, and 34 per cent indicate a normal tolerance. It must be remembered, however, that these glucose tolerance tests were not made in consecutive cases of hyperthyroidism but in picked cases; the tests were made because of the presence either of glycosuria or of hyperglycemia two and one-half or more hours after a meal. Moreover, 10 cases in this series were of colloid goiter without hyperthyroidism. Therefore these percentages do not represent an average incidence of impaired glucose tolerance in cases of hyperthyroidism, but rather the incidence in a selected group.

12. From the observations in these cases it would appear that the renal permeability is increased in the active stage of

hyperthyroidism. The renal threshold for glucose was below 120 in 35.6 per cent of the cases.

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PATHOLOGY OF GOITER

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Attempts have frequently been made to formulate a classification of goiters which should provide a separate group for all the various pathological and clinical entities. The more I study goiters the more I am convinced that the goiterous disease is a more or less continuous process, and the various pictures declare the state of development rather than a pathological or clinical entity. We should speak of the stages of goiters rather than of kinds. One does not have the proper mental equipment for the study of goiters unless he knows the life history of patients who run their course without treatment. Practicing in one community for a lifetime, I have been able to trace repeatedly the process from the adolescent colloid to the bossilated masses of middle life, and finally the cardiac decompensation and evidence of dysthyroidism. One of the chief difficulties lies in the proper interpretation of the clinical picture. The patients must be considered aside from the goiter in order that irrelevant symptoms may be properly classified. The condition of the patient following operation must be traced for an indefinite period. Indeed the study is not completed as long as the patient lives. It is only by keeping these facts in mind that one can predict from the clinical picture what the slide will show.

The simplest classification as heretofore published distinguishes two great classes of goiters. The colloid, characterized by the excessive collection of colloid with the subsequent development of accessory (possibly compensating) acini, resulting in a long line of various types of degeneration. This group is characterized by the excessive colloid content. In early life this appears as a more or less uniform enlargement, causing no considerable disturbance. In early maturity this gland becomes irregularly bossilated by the more rapid growth of certain areas. By successive remissions and exacerbations the development continues. Often the increased growth is associated with pregnancy or some other periodic disturbance. It is interesting to note in

this connection the comparative rarity of this type in the male. When this bossilated state is reached, the term adenoma has been applied. This is most unfortunate, for in no sense is the term "oma" applicable. The disturbance is in no wise tumorous, but always functional, and the nature of the functional disturbance can be read in the anatomical structure of the gland. There is everywhere evidence of failure and an effort to compensate for it.

In the other type there is a marked cellular proliferation, resulting in typical Graves' disease. The characteristic feature is marked cellular proliferation with or without actual papillary formation in patients who have eye signs. It is a mistake to assume that the whole gland is made up of this type of structure. As a matter of fact, those of us who have published such pictures have been obliged to search our slides to find such areas. The largest part of the slide is made up of far less active cellular proliferation. True, in a few the larger part of the gland is made up of papilla-bearing areas, but these are rare. In the great majority a part of the gland is made up of old colloid acini associated with the formation of new acini, with a greater or lesser number showing active cellular development, resulting in papillation.

The cause of the glandular increase is not known. Whether it ever is developed as a primary process or whether the cells are spurred to activity by a previous change, is not known. There is evidence that there are always previous changes. If so, this type may be but a type of the former. It is easier to conceive that some change in the colloid stimulated the cells to activity than that they just happened to develop. It is difficult to form an opinion, because the range of variation in the normal is little understood.

When a large number of goiters representing Graves' disease are studied, one finds the dividing line between the so-called toxic adenomas and the Graves' disease to be a narrow one. It represents an acute exacerbation, rather than a new or distinct process. Hence, instead of separating them from the old colloids, we contribute to clarity by considering them as a variation in the process. Hence, all goiters may well be considered as stages and variations of a single thyroid disease.

True enough, many cases of Graves' disease appear of sud-

den development in patients previously free from goiter. Much confusion has arisen because we have taken the patient's word as to the date of the appearance of a goiter. When a patient comes to us with a cancer of the breast the size of a walnut, and declares the tumor developed from a bump from a broom handle ten days previous, we are not misled. Yet when a patient comes to us and tells us that his goiter first developed a few weeks or months ago, we believe the statement. Yet on examining the gland in the laboratory we find old acini, newly developed acini, and vascular and tissue changes that must have required years to form. Many patients, of course, come with obvious goiters who never knew they were so afflicted. The patient's statement of the duration of a goiter is wholly valueless and must not be allowed to enter into the argument. A careful microscopic study of the gland, on the other hand, gives very accurate evidence. A superficial study is not sufficient. The changes in the acini and connective tissue must be studied by specific stains. Histo-chemistry must be brought to the aid of topographic pathology. In conformity with this conception, the following groups, therefore, are to be looked on as the various stages in the development of the goiterous disease, rather than separate types. We may mention them in the order of their occurrence.

Adolescent Stage.—This, as the name implies, is the goiter of early life. They are characterized by relatively large, elastic, often very soft, goiters, usually symmetrical in form. They usually do not markedly disturb the patient, but when nervous patients possess them toxicity may be simulated. The more I study patients with these early goiters, the more I am in doubt as to whether or not they ever are symptomless. The patient exhibits evidence of nervous hyperactivity and generally a pulse that is somewhat augmented. Even from the earliest beginning there are no innocent goiters.

Histologically, these glands show large acini filled with a homogeneous acidophilic colloid. Even in this early stage there is usually evidence of new gland formation in the interstitial cells or in the walls of the acini. A goiter made up wholly of large acini without any cellular activity is very rare. In the 1,000 glands on which this study is based there is not one example. True enough, areas large enough from which a photomicrograph

may be made are found, but when the whole slide is examined, or slides from various areas, cellular activity will most certainly be found in some parts of the gland.

As a corollary to this stage, it is necessary to consider the small, firm goiters which Goetsch and I have called interstitial goiters. There are found in girls and young women. The glands are small, symmetrical, and usually firm to the touch. It is unfortunate that these have been classed with goiters for they are usually associated with dysmenorrhea and intermenstrual pains. If they were regarded as they should be, as pluriglandular affections, there would be a greater likelihood of properly interpreting the lower abdominal pain and help us to understand the nature of the mythical "chronic appendix."

Microscopically these glands show some colloid increase, but it is for the most part unchanged. The acinal epithelium is flat. The interstitial cells are prominent, reminding one of the appearance of thyroids in children. In these there is no new gland formation.

Colloid Stage (Innocent Colloid). The old long standing goiters develop irregularities so that the goiter becomes bossilated. This irregularity of form is brought about by the development of some lobules more rapidly than others. If one has a chance to observe a goiter over many years one can note from time to time the appearance of some new bossilations.

These bossilations owe their restriction to the fibrous tissue septae which characterize the normal gland. On section these bossilations are seen to be made up of many small lobuli, each representing a lobule in the normal gland.

Histologically one sees that the increase in size of the lobule is dependent on the development of small acini in the interstitial cells or within the walls of the old acini. The cells lining the old acini are seen to be flat endothelial-like, while those of the smaller ones are cuboid, suggesting that these small glands are carrying on the function and really constitute a compensatory hypertrophy. The source of the new acini is unquestionably the interstitial cells and likely, in part, the walls of the old acini.

It is by this process that the goiter becomes lobulated. The large lobuli are usually made up of many smaller ones. These

smaller lobuli may undergo changes, each for itself, giving to the section a mottled appearance.

During this development the patient is but little disturbed by the gland, yet if the symptoms are studied carefully periods of nervousness, loss of weight and rapid pulse will be discovered.

Chronic Toxic Stage (Toxic Adenoma). Sooner or later the patient is compelled to recognize definite disturbance. When this stage is reached there may be notable change in the size or outline of the gland, or in its consistency. True, patients sometimes state that the glands have become larger recently. As a rule their complaints are not of any physical change of the gland but of general disturbance. They become nervous, lose weight, become sleepless, and have a rapid pulse, and the like.

Histologically, in the majority there is most often sign of cellular activity either in the newly formed acini or in the epithelial lining of the old acini. The cells of the acini are cuboid, seldom columnar. Many new acini are in evidence. Various areas of the gland nearly always still show the structure of the old colloid stages. It is only in certain areas that the cellular increase is marked. The goiter now has become a toxic adenoma, according to the generally accepted terminology.

In many of these there is no evidence of cellular activity but everywhere there is evidence of degeneration. This is notable particularly in those cases going on to a rapid death. What part degenerative processes play in the less active cases is difficult to say.

Acute Toxic Stage (Graves' Disease). These may begin rapidly in patients who did not know that they had previously had a goiter; nor does the surgeon, in many instances, until he has examined the gland in the laboratory; or the condition may be implanted on a known preexisting goiter. The clinical symptoms are characterized by greater intensity as well as more rapid onset. It is a matter of degree rather than of kind. If implanted on a known preexisting goiter we have the so-called Basedowified colloid, which, in the light of the present study, seems an inspired designation.

In the more intense types eye signs are present. In many patients one can predict that eye signs will develop. In general

the presence of eye signs indicates the severer types, but equally severe types are found without the presence of the eye signs.

Histologically this type is characterized by active epithelial proliferation. If one is to employ an oncological cognomen one could with good grace call these "adenomas," for in an active gland the imitation to a malignant adenoma is very close. The glands develop by forming new glands in the interstitial cells as well as the papillary projection of cells into the lumen of the acini. The cells are cuboid or cylindrical. In the very active cases the latter predominate.

In small glands the greater part may be made up of such active proliferating glands. In those developing on old colloids only certain areas are so affected. Since most of the acutely toxic glands are found in early life the glands are usually small and the evidence of old colloid change is not so prominent. It takes many years to produce an old lobulated colloid goiter. In the small glands, however, many acini are found which contain a vacuolated colloid. Recently this is ascribed to the use of Lugol's solution, notwithstanding the fact that the same picture was present before Lugol's was used. In no case in my experience is there evidence that a Graves' disease developed in a normal gland. It would appear warranted in assuming that the changes in the thyroid gland preceding the development of toxic symptoms is one of degree instead of one of kind.

The conception of all goiterous diseases as stages of one process facilitates the understanding that there are no innocent goiters and that all, sooner or later, will lead to toxic states jeopardizing the life of the patient.

SUMMARY

From a study of 1000 cases personally observed the following conclusions are drawn:

1. Goiters without evidence of new gland formation are rare.
2. The development of new acini is more or less progressive.
3. The exacerbation of this development comes sooner or later and is characterized by greater activity of the epithelium or some associated degeneration.

4. When the gland proliferation is very active the clinical symptoms are more pronounced but not essentially different in kind.

5. In view of the obvious shading of the various clinical and pathological pictures into one another it seems it would clarify our clinical conception, and lessen the burden of the pathologists, by considering the whole as one disease of which we can speak of stages, rather than of kinds.

ADDISON'S DISEASE WITHOUT PIGMENTATION: REPORT OF A CASE*

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Pigmentation is so constant and striking in Addison's disease that in its absence an unconfirmed clinical diagnosis will be accepted with reservations. Yet it is definitely known that Addison's disease does occur without pigmentation. The diagnosis can be made clinically and at times with considerable certainty as indicated in the following case:

REPORT OF CASE

A man, aged forty-five, born of Scotch parentage in the British West Indies, a hardware merchant in northwestern Canada, came to the Clinic, June 8, 1927, complaining of weakness, dizziness, dyspnea, and palpitation of ten months' duration. The symptoms during the last two months had become progressively more marked. His father died from typhoid fever, and his mother from an unknown cause at the age of fifty. The patient had been married seventeen years and had three children living; one child died in infancy from congenital lymphatic cysts. Aside from typhoid fever at ten and occasional colds, he had never been ill. He was said to have been a man of unusual energy.

In the summer of 1926, while working in his garden, he began to realize that he was weak and not in good physical condition. Back-ache developed readily and he said that it was a relief to sit down and rest. In October, 1926, what appeared to be neuritis of the brachial plexus developed and was treated by heat, massage and electricity. He did not improve satisfactorily and went to Honolulu for the winter, resting two months, with some benefit. He returned to work in April, but within a short time pain developed in the chest which incapacitated him for a week, and pleurisy was diagnosed. The following week he had two devitalized teeth removed, and subsequently an acute cold persisted for a week. During April he had "weak spells" which necessitated a two weeks' rest. Two weeks later, while walking home

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from his work, a distance of a mile, he felt faint, or "all in." He called his physician, who again advised rest. Subsequently he had not been able to stand any length of time without feeling faint and weak. He felt dizzy on changing from the recumbent to the upright position. This was accompanied by a peculiar feeling of sickness in the pit of the stomach. Shortness of breath and palpitation on exertion were noted. His appetite was fair, but the effort of eating tired him. There was considerable abdominal distress, with belching and flatulence after eating. He had lost 15 pounds in weight in two months. The joints became sore on walking. Some residue of neuritis in the right arm still persisted and he was restless and slept poorly.

Physical examination revealed a weak, restless man, 5 feet 10.5 inches tall, weighing 140 pounds. The tonsils were small and buried. The heart sounds were distant and slightly irregular. The lungs were normal except for slight dullness and slightly decreased fremitus anteriorly and posteriorly over the left upper lobe. Roentgen-ray examination of the chest disclosed no abnormal condition. The abdomen was normal to palpation. The pulse was 92, temperature 97, systolic blood pressure 86, and diastolic 64. The condition was regarded as probable postinfectious exhaustion. The low blood pressure and the dizziness on standing suggested postural syncope or postural hypotension. Because of the extreme weakness, further examination in the Clinic was deemed unadvisable and he was admitted to the hospital for further study.

In the hospital, ephedrine, which has been found of decided value in certain cases of postural hypotension, was tried, but without favorable results. The heart sounds were poor in quality, extremely faint and heard better with the naked ear than with the stethoscope. The blood pressure continued to be about 80 systolic, and 50 diastolic, until the sixth day, when it reached the low level of 68 systolic and 48 diastolic. Addison's disease was suggested and a most careful search made of the skin and mucous membrane for evidence of pigmentation. The man's complexion was decidedly ruddy and showed no evidence of tanning or darkening of the skin, even in the exposed areas. There was an occasional dark freckle over the face and neck, but there was not the slightest trace of pigmentation of the mucous membranes. Despite the absence of pigmentation and the ruddy complexion, a diagnosis of Addison's disease without pigmentation was made from the clinical picture.

An observation of unusual interest was the depressed, canal-like groove of the frontal vein, descending over the forehead. This venous canal could be filled when the head was in the dependent position, but was replaced by an excavated depression or groove with the patient in a normal position, lying, sitting or standing.

The patient was placed on a mild Muirhead regimen on which he did poorly. At the end of a week this was discontinued, because it was felt that he evidenced an actual intolerance to adrenal products.

All drugs, aside from hypnotics, such as allonal and phenobarbital (luminal), which were required for sleep, were discarded. Blood pressure continued to decrease and clinical improvement was lacking. A second trial of the Muirhead treatment was made, using very small doses of epinephrin, but, aside from slight increase in blood pressure, no improvement was manifested.

Abnormal changes in blood pressure relative to posture were exhibited by this patient. When his position was passively varied while lying on an adjustable table, each fractional raising of the head from 45 degrees below horizontal to the perpendicular upright position resulted in a step-like fall of the blood pressure from 80 systolic and 60 diastolic (head down) to 60 systolic and 54 diastolic (head upright). Mortensen's* series of ninety normal women exhibited an average mean fall in blood pressure of 4 mm. systolic and an average mean rise of 8 mm. diastolic during essentially the same passive changes in posture. The pulse rate of the patient increased from 72 (horizontal) to 90 when passively changed to the upright posture, which is a considerably higher rise than the average mean rise of 10 pulse beats a minute which Mortensen's ninety normal women exhibited. The same observations of pulse and blood pressure, made in a typical case of postural hypotension with syncope, revealed an abnormal, step-like fall of blood pressure from 128 systolic and 98 diastolic (horizontal) to 56 systolic and 40 diastolic (upright), while the pulse rate remained unchanged.

The patient became progressively weaker, irritable and restless. Voluntary lifting of his head or extremities from the bed surface soon required visible effort. All food was distasteful and seemed to disagree. A sighing sort of respiration developed and became more marked, a tracing indicating it as a true Biot type.† The urinary output began to decrease at the end of the first week, dropping from 2400 cc. to 800-1000 cc. The phenolsulphonaphthalein output decreased from 60 per cent to 30 per cent. The blood urea mounted from normal until it reached the level of 89 mgm. for each 100 cc., while the blood sugar remained at from 0.092 to 0.12 per cent. There was no cytologic change in the blood. The basal metabolic rate was -9 and gastric analysis showed total acidity, 44, and free hydrochloric acid, 32. At this time the patient was so weak that his voice became husky and muffled, with slurring of the syllables. Decubitus appeared in the left ear. He was clear mentally except for slight fogging just before death. On the last day he became somewhat cyanotic. He was given glucose solution intravenously, a small transfusion, and oxygen from an oxygen tent. Under the latter treatment he breathed with greater comfort and slept. Respiration decreased to 6 and 8 a minute, and coma and death followed.

Necropsy was refused, but a limited examination for the purpose of determining the presence or absence of tuberculosis was permitted.

*Mortensen, M. A.: Blood pressure reactions to passive postural changes. *Am. J. M. Sc.*, 1923, 105, 667-675.

†This type of respiration has been noted previously by one of us (Rowntree).

The pathologist's report was tuberculosis of the suprarenals, Addison's disease, healed tuberculosis of the left lung, hilus nodes and pleuras; emaciation was graded 2.

This patient, therefore, represents a case of Addison's disease resulting from tuberculosis of the suprarenals in which the clinical course was typical in every respect, except for the absence of pigmentation. The course was rapidly and continuously downward. The patient was not benefited by epinephrin and adrenal cortex, but appeared, in fact, intolerant to them. The diagnosis was made clinically and was confirmed by pathologic examination. Such cases as this are rare.* This represents the first instance of "Addison's disease without pigmentation" confirmed pathologically in the Mayo Clinic, although more than seventy cases of Addison's disease have been observed and studied.

*A case was observed previously in the Clinic in which, in the absence of pigmentation, the diagnosis of Addison's disease was made clinically. Since necropsy was refused, confirmation was not possible. In that instance, also, the downward course was progressive and considerably more rapid than is usual in Addison's disease.

A CASE OF PHYSIOLOGICAL CASTRATION IN THE FOWL

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Much of the knowledge of the relations which the functioning reproductive glands bear to somatic development has been gained from operative experiments. However, in some cases, abnormal individuals have been observed which have provided evidence concerning these relations. There came to our notice some time ago a case in the latter group. A Plymouth Rock cock had been purchased from a high grade pen for breeding purposes. To all appearances the bird was a normal young male but before he had reached the breeding age he came gradually to resemble a capon. Especially were the development of his comb and wattles, and the general shape and appearance of the body characteristic of a castrated bird.

Unfortunately the bird died in the pen several hours before we had the opportunity to examine him. No notes were available concerning his behavior except that we were told by the owner that he acted like a capon and was driven about by the other birds of both sexes.

Post-mortem examination gave evidence that the bird had died of a disease which had been progressing for some time. The whole body was emaciated and there were no fat deposits such as are characteristic of healthy birds. Many of the organs seemed to be more or less involved, as several were found with small caseous nodules varying in size up to 7 or 8 mm. in diameter. Microscopic examination failed to give evidence of bacterial invasion. In some cases these nodules seemed to be characterized by increased amount of connective tissue and were richly infiltrated with blood.

The gonads were the subject of special attention. They were much smaller than those of a healthy bird, the left measuring 14x5 mm., the right 13x6 mm. A microscopical examination also showed the testes to be very abnormal. Spermatogenesis was practically lacking. The tubules in the peripheral one-third

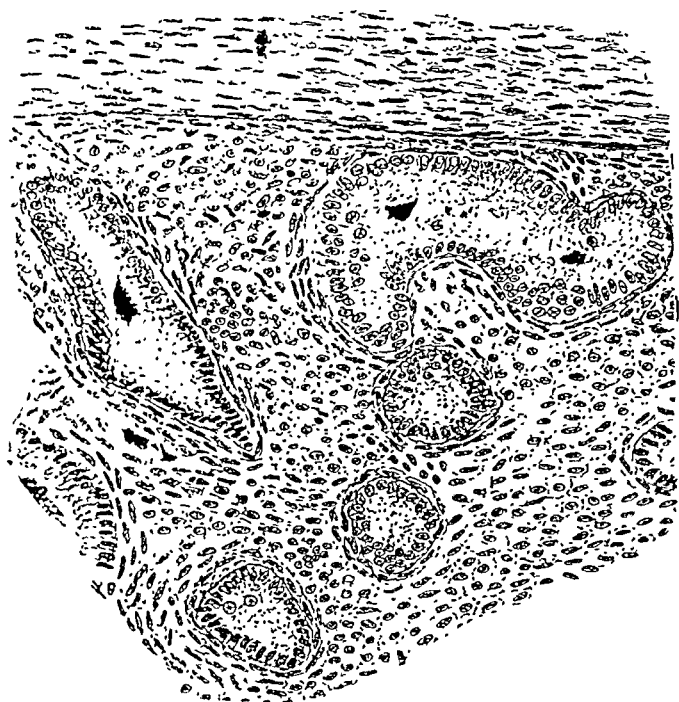


Figure A. Camera lucida drawing of portion of peripheral region of testis.



Figure B. Camera lucida drawing of portion of central region of testis.
Compare with Figure A.

of the radius of the testes were markedly degenerated and somewhat wrinkled in contour, while the inter-tubular spaces were wide and more or less filled with spongy connective tissue (Figure A). The large number of red blood corpuscles indicated an inflammation. Toward the center of the cross-section the tissues appeared less abnormal. The tubules were close together, rounded, with smooth contours, and the amount of inter-tubular substance, both connective tissue and blood cells, appeared to be much less than in the peripheral layer (Figure B). In neither zone were found typical "interstitial" or "luteal" cells. The peripheral zone of degenerated and wrinkled tubules seemed to be proportionately wider in the left testis than in the right.

The cells of the tubules toward the periphery of the testes were, as far as spermatogenesis is concerned, inactive. Scarcely a mitotic figure was found. In the main these tubules had a single layer of spermatogonia and Sertoli cells with few, if any, spermatocytes. The spermatogonia were somewhat longer and narrower than the spermatogonia in tubules having one or more generations of spermatocytes. The more centrally located tubules were different. Usually in addition to the basal layer of spermatogonia there were one or two layers of spermatocytes. These spermatogonia more nearly approached the appearance of the spermatogonia of normal testes except for the fact that multiplication divisions were scarce. Maturation divisions also were few.

That the abnormal structure of the testes had hindered their normal functions is unquestionable. That the impaired functions of the gonads had reacted on somatic development, especially on the development of the secondary sexual characters, seems quite probable. The effects were similar in many respects to those following gonadectomy. The bird had the appearance of a capon. What had happened seemed to be a case of physiological castration.

The question arises, as it does in any consideration of the relation of the male sex glands to secondary sexual characters, what part of the testis effects the development of these characters? Are there certain determinable parts of the glands which, acting as endocrine organs, secrete a substance which stimulates the growth and development of comb and wattles, and modifies more or less bodily development and psychic behavior? It would

seem so, since removal of the entire glands results in profound bodily changes.

To certain cells in the inter-tubular material have been attributed the function of acting as ductless glands the secretion of which stimulates development of the secondary sexual characters. The fact that ligation of the vas deferens in birds results in atrophy of the seminiferous tubules and in a retention of, or possibly an increase in the normal amount of interstitial material, while the normal sexual characters are retained (Massaglia, 1921)*, indicates that these interstitial glands function in controlling secondary sexual characters.

The case of the bird under consideration, however, differs from the experimental cases. The gonads of the abnormal bird showed marked degeneration of the convoluted tubules and an increase in inter-tubular material, a condition similar to those produced by the ligation experiments. Coincident with these histological abnormalities was lack of development of some of the secondary sexual characters, a condition just the opposite of those resulting from ligation of the vas deferens.

This would seem to indicate that the inter-tubular material was not responsible for the development of comb and wattles, but rather that the spermatogenic or Sertoli cells might have had some role in controlling the growth and development of some of the secondary sexual characters. Such an idea has been advanced by Loisel (1902).

Not only is the idea of the endocrine function of spermatogenic tissue suggested by the present case, but the fact that in most cases of birds in which the male is more brilliantly colored, the intensity of color is heightened during the mating season, at which time the spermatogenic tissue is more active. That some endocrine function may be attributed to other parts of the male reproductive gland is admittedly possible, but that the cells of the convoluted tubules may serve as glands is also likely. Further investigation of these tissues by improved cytological methods may aid greatly in solving this perplexing problem.

*No attempt has been made to present a list of references since a comprehensive bibliography is given in Lipschutz, 1924, "The Internal Secretions of the Sex Glands." Williams and Wilkins, Baltimore.

Abstract Department

The effect of lowering blood pressure on myocarditis caused by epinephrine hydrochloride and caffeine in the rabbit. Barksdale (E. H.), Arch. Path. & Lab. Med. (Chicago), 1927, 3, 658-660.

Lesions of the myocardium had been previously observed following a single injection of epinephrine hydrochloride and caffeine. Barksdale in the experiments here reported undertook to determine the relation of the increase in blood pressure caused by the injection to the lesions found. He employed two methods for preventing the rise in blood pressure: (1) bleeding combined with the inhalation of amyl nitrite; and (2) the injection of sodium nitrite followed by inhalation of amyl nitrite. It was not found possible by either of these methods to prevent the increase in blood pressure, but both greatly hastened the return of the pressure to normal. Eighteen control animals lived as long as six to seven days after the injection of epinephrine and caffeine and all showed the characteristic lesion in the wall of the left ventricle near the auriculo-ventricular groove. Twenty-five animals, in which an attempt was made to prevent increase in blood pressure, lived as long as six to seven days after the injection of the epinephrine, and only fifteen, or 60 per cent, showed the lesion in the wall of the left ventricle. It appears, therefore, that the diminution in the duration in the action of epinephrine and caffeine prevented the production of the myocardial lesions in 40 per cent of the animals used. Barksdale concludes that in all probability the mechanical effects of the high blood pressure induced by the injections of epinephrine and caffeine are essential factors in the production of the myocardial lesions which follow such injections.—J. P. S.

On carbohydrate metabolism of adrenalectomized rats. Cori (C. F.) & Cori (Gerty T.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1927, 24, 539-541.

Rats which have survived adrenalectomy show a decreased blood sugar after twenty-four hours' fasting. This is due to a lack of reserve glycogen in the liver. Such rats form glycogen from glucose at a normal rate. It is suggested that a disturbance in the formation of glucose from protein due to lack of adrenin or cortical material occurs. Experiments on adrenalectomized rats and mice

show that the inhibition of glycogen formation in the liver which follows injection of insulin is not due to adrenin.—J. C. D.

Anatomy and histology of the interrenal bodies of man (Beitrag zur Anatomie und Histologie der Interrenalkörper des Menschen). Iwanoff (G.), Ztschr. f. Anat. u. Entwicklungsgesch. (Berl.), 1927, **82**, 368-387.

The study is based on 132 bodies from newborn to 70 years of age, several fetuses 18-25 cm. long and a couple of animals. The retroperitoneal space along the abdominal aorta contained from 1 to 5 adrenal bodies in 60 per cent of the cases. They were most numerous on the right side. They varied in size from a millet seed to .5 x 5 cm. and are elongated in shape. Transitional forms between accessory adrenals and true isolated paraganglia were found after the second year. When they are associated with a well developed connective tissue capsule they were frequently infiltrated with lymphoid elements, mostly small lymphocytes, in the form of ill defined islands. There is a description of a central vein which is looked upon as the avenue by which the incretion leaves the gland.—A. T. R.

Influence of different diets on the nucleo-plasma ratio in the cells of the suprarenals of rats (Messungen an den Nebennierenzellen der Ratte. Einfluss verschiedener Ernährung auf die Kernplasmarelation). Kolliner (Martha), Ztschr. f. Anat. u. Entwicklungsgesch. (Berl.), 1927, **82**, 1-21.

Ten rats weighing in the neighborhood of 100 grams each and 2 rats weighing 60 to 70 grams each were divided into six pairs, each pair consisting of a male and a female animal of approximately the same weight. Each pair was given a different diet for about three months. In general these diets caused a considerable increase in body weight except wheat alone where the body weight remained near or only slightly above the initial weight. The nucleo-plasma ratio of the cortical cells in a wheat and cod liver oil diet was small, while in a pure wheat diet this ratio was relatively large. In a diet of wheat and yeast many cells in the cortex (except in zona glomerulosa) had a small nucleo-plasma ratio. In a diet of wheat and 1% calcium the cells in the cortex and medulla had a relatively large ratio, except in the outer part of zona fasciculata where the ratio was smaller than the average. In a diet of wheat, cod liver oil and calcium there was in general a smaller ratio than with a wheat and calcium diet. With a wheat and lemon juice diet the ratio in zona fasciculata was below the average and in the medulla it was distinctly larger. However, the number of animals in each group is too small for trustworthy generalizations.

—A. T. R.

A report of two cases of adrenal insufficiency (Addison's disease).
Medlar (E. M.), *Am. J. Path.* (Boston), 1927, 3, 135.

On the basis of the pathological changes found in the adrenals, cases of Addison's disease may be divided into two groups: (a) the more common form in which there is extensive destruction of adrenal tissue by tuberculosis, tumor growth, etc.; and (b) a rarer form of essential or idiopathic adrenal insufficiency in which neither infection nor neoplasm plays any part. The two cases reported by Medlar belong in the latter group. Case 1, concerned a man 28 years of age who was ill for only one week, with weakness, pigmentation of the skin, vomiting, etc. The chief findings at autopsy were status thymico-lymphaticus and atrophy and fibrosis of the adrenals. The second case was that of a woman aged 29 years, who had had a progressive pigmentation of the skin for two years and otherwise ran a more typical course of Addison's disease. At autopsy there were found: marked atrophy and destruction of adrenal tissue associated with hyperplastic lymphoid tissue; old rheumatic endocarditis; old healed bilateral pulmonary tuberculosis; bronchopneumonia, and hyperplastic islands of Langerhans. Medlar is of the opinion that these two cases emphasize the association between status lymphaticus and hypofunction of the adrenals; he suggests that status lymphaticus is an expression of an attempt on the part of the body to correct a deranged metabolism brought about by a paucity of adrenal secretion.—J. P. S.

A case of adrenal adenoma. Merriam (J.) & Smith (L. W.), *Boston M. & S. J.*, 1927, 197, 135-137.

The tumor was successfully removed. The patient had no systemic disturbances.—J. C. D.

The organization of experimental adrenal cell emboli in the lungs.
Simonds (J. P.), *Am. J. Path.* (Boston), 1927, 3, 13.

Rabbits were injected intravenously with a rather coarse emulsion of dog adrenals. There are certain resemblances between the histologic tubercle and the nodules produced in the lungs of rabbits by the organization of the emboli produced by these injections. This peculiar type of reaction is believed to be due to the high content of lipoid substances, especially cholesterol, contained in the adrenal cells.—Author's Abst.

Influencing peripheral action of epinephrine by extracts of organs.
Steppuhn (O.), & Sargin (K.), *Arch. f. exper. Pathol. u. Pharmacol.* (Leipz.), 1926, 112, 1-16.

An experimental paper containing a cut of the apparatus used, 5 curves and 3 tables of the essential observations. In spite of

much work the relation of the endocrine glands to the origin and course of labor in childbirth has not been solved. It has been observed that extract of the placenta has increased the uterine contracting power of adrenaline. An increased amount of adrenaline was found in the blood of gravid animals. The rôle of the placenta in childbirth may be greater than previously assumed. Using the isolated rabbit ear method of Krawkoff, these authors found that placenta extract, 1:500, caused a diminution of 70% in the number of drops flowing through the ear. Various other extracts gave similar results. With the guinea pig's uterus they observed contractions three or four times greater when placenta extract plus hypophysis extract was added than when hypophysis extract alone was used.—E. L.

Transplantation and individuality differential in strains of inbred rats. Loeb (L.) & King (Helen D.), *Am. J. Path.* (Boston), 1927, 3, 143.

The results of homoio-, syngenesio- and auto-transplantation of thyroid, parathyroid, etc., in non-inbred rats were compared with those obtained in rats that were the product of long continued inbreeding by means of successive brother and sister matings. The data obtained from these experiments indicate that in contrast to the results obtained in inbred guinea pigs, where inbreeding led to a marked decrease in the intensity of the reaction and where the individuality differentials became very similar (although not yet identical through inbreeding), in the rat successive brother and sister matings, continued through many generations, do not lead to a marked increase in similarity of the individual differentials in the inbred animals.—J. P. S.

Syngenesiotransplantation in the guinea pig. Loeb (L.), *Am. J. Path.* (Boston), 1927, 3, 29.

Loeb studied transplants of thyroid and parathyroid in guinea pigs. Syngenesio-reactions in this animal have a position intermediate in character between homoio- and auto-reactions. This intermediate character is due to the variations in individual reactions which approach auto-reactions on the one hand, and homoio-reactions on the other hand, as well as to a real intermediate syngenesio-reaction. The typical syngenesio-reaction resembles the auto-reaction as far as the behavior of the connective tissue and vessels is concerned. It differs from the auto-reaction in as much as subsequently lymphocytic masses invade the transplant. Brother to brother transplantations resemble autotransplantation to a higher degree than parent to children or the reciprocal transplantations. The grade of transplantations from parent to offspring does not seem to be significantly higher than the grade for the reciprocal

transplantation. Transplantations between grandparents and grandchildren have average higher grades similar to those of transplantations between parents and children. Relationship or dissimilarity (race differences) between the two parents seems to influence the intensity of reactions in the exchange of tissues between the various members of families.—J. P. S.

Syngenesiotransplantation in the rat. Loeb (L.), *Am. J. Path.* (Boston), 1927, 3, 45.

Loeb transplanted thyroid, parathyroids and parts of other organs into rats. Syngenesiotransplantation in the rat shows an intensity of reaction which is intermediate between the reactions in auto- and homoio-transplantations. In both guinea pig and rat the average of individuality differentials of donor and host shows the smallest discrepancy in brother to brother transplantations; it is greatest in parent to children or children to parent transplantation. In general the reactions against syngenesiotransplantations in the rat are less severe than those in the corresponding syngenesio-transplants in the guinea pig. This condition is probably due to a greater homogeneity in the genetic composition of the rats than of the guinea pigs used by Loeb. The reactions against pieces of different organs derived from the same donor are relatively of the same strength because of the identity of the individuality differentials, although absolutely the reactions differ. The differences are due to secondary factors. On the basis of these secondary factors we may distinguish: (a) organs like the thyroid and parathyroid (in which variations in intensity of lymphocytic and connective tissue reactions cause the main differences in the fate of transplants); (b) organs like the ovary (in which, while the lymphocytic reaction occurs, it is usually not very pronounced, but in which under the influence of very severe homoio-toxins only the more resistant component parts of the organ survive); (c) less resistant tissue like bone marrow, striated muscle tissue and to some extent also non-striated muscle tissue (the latter tissue survives or regenerates completely after transplantation for a longer period only in the absence of the more severe homoio-toxinism) and (d) very resistant tissues like cartilage and perichondrium.—J. P. S.

Significance of pseudoepiphyses in endocrinology (*Über die Pseudoepiphysen und deren Bedeutung in der Endocrinologie*). Rochlin (D. G.), *Ztschr. f. Anat. u. Entwicklungsgesch.* (Berl.), 1927, 82, 354-367.

As a rule there is no epiphyseal ossification center on the distal end of the phalanges, first metacarpal and first metatarsal bones or on the proximal end of the second, third, fourth and fifth metacarpal and metatarsal bones. A more or less independent ossifica-

tion center in any of the above locations gives origin to what is termed a pseudoepiphysis. Pseudoepiphyses are more frequent in infantile retarded development and apparently where the endocrine disturbance is pluriglandular. Hypothyroidism seems to play a large rôle. Usually there is also hypogenitalism, but the sex glands are not considered to be a cause of the pseudoepiphyses. A pseudoepiphysis is especially frequent on the middle phalanx of the fifth finger. Bones with a pseudoepiphysis are usually too short. Pseudoepiphyses were not encountered in cases of excessive growth of bones in length nor in cases of accelerated differentiation as, e.g., in Basedow's disease and pubertas praecox. The report is based on 40 original cases with pseudoepiphysis, 32 of which were especially selected. The anomaly was present in 5.2% of children from 2 months to 10 years of age.—A. T. R.

Cyclic changes in the ovary of the mole (*Untersuchungen über das Ovarium von Talpa europaea mit besonderer Berücksichtigung seiner cyclischen Veränderungen*). Altmann (F.), *Ztschr. f. Anat. u. Entwicklungsgesch.* (Berl.), 1927, 82, 482-569.

Serial sections of the ovaries of 98 specimens, representing every month of the year, were analyzed by projecting them on paper at various magnifications and then weighing the paper representing the various constituents. Thirty-one of these animals were killed in March during the active sexual period and pregnancy. The interstitial cells decrease greatly during the active sexual period in the spring. This and the other elements in the ovary are discussed from the standpoint of their probable rôle in the sex cycle—A. T. R.

Action of follicular fluid on uterine contractility. Brouha (L.) & Simonnet (H.), *Compt. rend. Soc. de biol. (Par.)*, 1927, 96, (2), 96-97.

When the resting uterus of the rat in vitro shows only small contractions, addition of fresh liquor folliculi (or extracts of it) augments the amplitude of contractions. With the guinea-pig uterus tonus is increased without inducing contractions. The question is raised as to whether the follicular hormone acts directly upon the uterine musculature in vitro.—E. A.

Female sex hormone, Menformon (*Ueber weibliches Sexuahormon im bes. das Menoformon*). Laqueur (E.), *Klin Wchnschr.* (Berl.), 1927, 6 (9), 390-396.

A summary of the author's contributions to this subject with references to other recent work. Laqueur's product, Menformon, is a clear water soluble preparation standardized at 10 mouse units

per mgm. It is readily dialysable, quite thermostabile and resistant to action of acids and alkalis. The principal animal reactions are: in females, growth of the vagina and uterus; in males, inhibition of growth of the testes and external genital organs. It induces an increase in rate of metabolism and has no harmful circulatory effects. Its therapeutic possibilities are discussed. The author considers the question unsettled as to whether one or several hormones are involved in female sex phenomena.—E. A.

A qualitative indicator for the testis hormone. Moore (C. R.), *Proc. Soc. Exper. Biol. & Med. (N. Y.)*, 1927, 24, 847-848.

In guinea pigs after removal of one testis the spermatozoa in the epididymis of the operated side retain motility for 60 days. If both testes are removed, i.e., all source of testicular hormone eliminated, motility is lost in about one-half this time.

Studies on the internal secretion of the ovary. IV. The significance of the occurrence of oestrin in the placenta. Parkes (A. S.) & Bellerby (C. W.), *J. Physiol. (Lond.)*, 1927, 62, 385-396.

Extracts were made (details given in original paper) from placentae of seven pregnant sheep, ten cows and thirty-six humans, also from amniotic fluid from sheep and cows, from whole sheep fetuses and from pregnant uteri of sheep and cow. In all the three latter sources small amounts of oestrus-producing substance were found. The placental preparations gave comparatively large yields. Where separate extractions were made from maternal and fetal placentae, oestrin was fairly equally divided between the two. The authors believe their results suggest that oestrin in the placenta is due to withdrawal from maternal circulation and not to elaboration by the placenta itself.—C. I. R.

Catabolism of sex glands in a case of pseudohermaphroditism (*Über den Geschlechtsdrüsen abbau bei einem Fall von Pseudohermaphroditismus*). Rinck (H.), *Ztschr. f. Konstit. (Berl.)*, 1927, 13, 209-211.

The description is given of a three-and-a-half-year-old girl with an abnormally long clitoris without an opening and having the appearance of a glans penis with the foreskin pulled back. The labia majora had the appearance of a scrotum. The internal organs were apparently those of a normal female and in some respects she acted like a girl (played with dolls, e. g.), but was rough and ill-mannered like a boy. Physical measurements are given. Abderhalden's serological catabolic test was made 8 times by the Hirsch interferometric method and showed that the testicular reaction was stronger than the ovarian, while the reverse is true of normal girls.—A. T. R.

not impossible that these centers or tracts are involved in the control of insulin secretion.—H. J. J.

A quantitative study of the hypophysis of the human anencephalic fetus. Covell (W. P.), *Am. J. Path.* (Boston), 1927, 3, 17.

Covell found hypophysis tissue in each of the 32 human anencephalic fetuses examined. The weight was very variable, and when corrected for vascularity it was usually less than the corrected weight of the hypophysis of normal fetuses of the same age. The pars nervosa was lacking in the majority of cases; when present at all its relative and absolute volumes were considerably less than those of the normal. The pars intermedia was variable both in occurrence and volume; it might be present in a gland in which the pars nervosa was absent. The pars anterior comprises most of the gland volume and apparently the total gland volume in many instances. The average relative volume of blood present in the anterior lobe is about 39% of the volume of that lobe.—J. P. S.

The effects of feeding anterior lobe pituitary extract to children. Gardiner-Hill (H.) & Smith (J. F.), *Lancet* (Lond.), 1926, 211 (5370), 219-222.

The authors report in this paper the results of administering anterior lobe pituitary extract (Armour) to under-developed children. Three types of cases were included: first, children with infantilism and defective growth; secondly, older female children with minor degrees of this condition accompanied by disturbances of menstruation; and thirdly, children with obesity of the apparently endogenous type. Two representative cases of each type were studied ranging in age from 9 to 19 years. A common metabolic disturbance in the form of a lowered sugar tolerance occurred in the first two groups before treatment. There was a slightly increased tolerance in the third. Bone development was definitely delayed as shown by X-Ray. The sella turcica was essentially normal in size in all cases. The effect of giving from 3 to 15 grains of extract daily was to produce a demonstrable increase in the sugar tolerance in every instance. The cases showing infantilism were found to gain in both height and weight at a rate greatly exceeding the normal. Menstruation became regular after treatment in one case of secondary amenorrhea, but was not affected in another in whom it had never occurred even at the age of 19 years. The obesity was unaffected in those cases in which it was a factor.—I. M.

Influence of pituitrin on diuresis variously induced. Knowlton (F. P.), Curtis (A. N.) & Silverman (A. C.), *Proc. Soc. Exper. Biol. & Med.* (N. Y.), 1927, 24, 865-869.

The authors conclude that when diuresis is induced in anesthetized rabbits by the method of continuous intravenous injection pituitrin acts to augment such diuresis. The effects are similar with various diuretics and with varying dosage and administration of the pituitrin. A table of results is included.

Dystrophia adiposogenitalis in three brothers (Familiares Auftreten von Dystrophia adiposogenitalis bei drei Brüdern). Rahlfs (S), *Ztschr. f. Konstit. (Berl.)*, 1926, 12, 758-778.

The author describes three sons of a syphilitic father. There were no signs of tumors of the hypophysis in any of them. Two showed dwarfism, which is taken to indicate some involvement of anterior lobe of the hypophysis. Intelligence was normal and the Wassermann negative in all.—A. T. R.

Preferential utilization of carbohydrate in diabetes. Campbell (W. R.) & Markowitz (J.), *J. Clin. Investigation (Balt.)*, 1927, 4, 37-52.

The authors studied the question of preferential utilization of carbohydrates (levulose, insulin, dihydroxyacetone, glycerine) in completely depancreatized dogs which were given a definite number of units of insulin before and throughout the test. Their results published in tables show no evidence that greater quantities can be utilized by the diabetic organism than of glucose itself, which fact suggests that these substances must pass through a glucose phase in their metabolism and therefore do not undergo any preferential utilization as compared with other carbohydrates.—H. J. J.

Synthalin—Substitute for insulin for oral medication (Über synthetisch dargestellte Körper mit insulinartiger Wirkung auf den normalin und diabetischen Organismus). Frank (E.), Nothmann (M.) & Wagner (A.), *Klin. Wchnschr. (Berl.)*, 1926, 5, 2100-2107; *Abst., Am. J. Med. Sci.*, 174, 278-279.

The authors report a synthesised product, called synthalin, which is an alkaline guanidin derivative. It lowers blood sugar and can be taken by mouth. When given to rabbits which have been starved 24 hours, in doses of 3 to 4 mgm. per kgm., it reduces the blood sugar to the point of convulsions. These are immediately relieved by the injection of glucose. In depancreatized dogs synthalin given in sufficient quantities causes a cessation of the glycosuria and lowers the blood sugar to the borderland of convulsions. In human diabetics it may cause the disappearance of 30 to 40 gm. of glucose from the daily output of urine. Its action is more delayed than that of insulin, being retarded sometimes as long as 24 hours, but it continues over a longer period of

time. It may produce, even in therapeutic dosage, a loss of appetite, rapid peristalsis, nausea and possibly vomiting. The authors recommend, therefore, commencing with small doses and working gradually up to what is necessary. When it is desired to change from the insulin treatment to the newer synthalin it is recommended also that both drugs be given at the same time, and that the amounts of synthalin be slowly increased while at the same time one lowers the dosage of insulin correspondingly. They conclude that this preparation lowers the sugar in the urine, 1 mgm. taking care of 1.1 to 1.2 gm. of sugar; that the blood sugar is brought down below the point where glycosuria occurs; that acidosis is relieved; that other symptoms of diabetes, such as polyuria and polydipsia, are removed. It is found useful in cases with temporary infection or those that are "insulin refractory": in diabetics with surgical infections, such as gangrene, furunculosis and phlegmons, it may be used in place of insulin. The contraindications for the use of synthalin are severe acidosis and diabetic coma, when the more powerful and more rapid action of insulin should be depended on until the emergency is past.

Rôle of vitamins and insulin in nutrition. Funk (C.), Paris méd., 1927, 61, 389-392.

A history of the vitamins and a review of the author's recent work on insulin is given in this paper. A new classification of the vitamins is also suggested. The vitamins proper are substances containing nitrogen and are very sensitive to alkali. They are named as follows: B—anti-neuritis, C—anti-scorbutic, D for the growth of micro-organisms and P for the prevention of pellagra. The vitasterols or vitasterines are characterized by not containing nitrogen and being very sensitive to oxidation. Vitasterol A is anti-xerophthalmic, E is anti-rachitic and F is necessary for reproduction. Substance A, which represents the pancreatic hormone, causes a lowering of the blood sugar in a diabetic, but in a normal individual there is no effect. The reason for this action is that substance C, or co-insulin, is necessary for the activation of A. In the normal being, A and C are present in proportional amounts. Therefore the introduction of an excess of A will not decrease the blood sugar because it is not activated. In a diabetic there is an excess of C, and A upon its introduction is promptly activated and then reduces the blood sugar. Substance B, an anti-insulin, has also been isolated from the pancreas. This substance will cause hyperglycemia and pancreatic disturbances.—E. L.

Diabetes refractory to insulin. Häusler (H.) & Höglér (F.), *Klin. Wchnschr. (Berl.)*, 1927, 6, 541-543.

Experiments were conducted with the blood corpuscles and blood plasma of normal, diabetic and insulin refractory diabetic persons. From their work these investigators came to the conclusions that the blood plasma of the insulin refractory person does not have the power to bind glucose, but that the glucose binding is done by the blood corpuscles. This glucose binding power can be removed by repeated washings of the corpuscles.
—E. L.

A clinical study of substance A isolated from insulin. Landsberg (M.), *Progrès méd. (Par.)*, 1927, 54, 242-245.

A preliminary communication reports the results with substance A on the blood sugar of both normal and diabetic persons. When 1.2 mgm. (equivalent to 20 units of insulin) was injected into a series of ten diabetics there was a fall in the blood sugar varying from 41 to 109 mgm. The oral administration was ineffective. When normal individuals received the same dose there was an increase of 4-35 mgm. in the blood sugar in five cases and a decrease of 4 mgm. in one case.—E. L.

Depancreatized dogs kept alive several months with insulin administered by stomach tube. Murlin (J. R.), *Proc. Soc. Exper. Biol. & Med. (N. Y.)*, 1927, 24, 549-550.

Insulin in ox-blood serum was used. Its effects on respiratory metabolism were immediate, and persisted for twenty-four hours or more. Daily doses kept depancreatized dogs alive for from six weeks to four months.—J. C. D.

Studies on the islands of Langerhans in human pancreas. I. The relation of the islands to the surrounding structures. Otani (S.), *Am. J. Path. (Boston)*, 1927, 3, 1.

This paper is a contribution, copiously illustrated with photomicrographs, to the still disputed question of the relation of the islands of Langerhans to the surrounding tissue of the pancreas. Otani's study is based upon the examination of the pancreas in each of 46 cases ranging in age from 3 days to 76 years. Silver impregnation was the staining method used. Three types of islands were recognized in the normal pancreas: (a) islands connected with surrounding acini, found in every case; (b) islands connected with interlobular and intralobular ducts; and (c) islands strictly separated from the surrounding structures. The islands have no

fibrous capsule of their own, but a more or less complete separation is produced by the basement membrane of the acini or ducts or by the interlobular connective tissue. There are wide variations in size, shape and relation of the islands to the surrounding pancreatic structures. Such differences are present not only in the same organ but even in the same sections. Therefore it is improper to speak of one regular type of island of Langerhans in respect to this relation.—J. P. S.

Studies on the islands of Langerhans in the human pancreas. II. Significance of variation in structure. Otani (S.), *Am. J. Path.* (Boston), 1927, 3, 123.

This paper is concerned with the significance of the varying types of islands of Langerhans described by Otani in a previous paper. The process of hypertrophy of these islands in adult pancreas is chiefly due to transformation and hyperplasia of acinar and centroacinar cells, the hyperplasia of the island cells, proper, being relatively insignificant. The acinar cells are able to change into island cells; whether the reverse change can take place is uncertain. Direct contact between islands and acini indicates a genetic relation. One type of island connected with ducts is interpreted as a remnant in the postembryonal pancreas or as resulting from the transformation from acinus to island cells, while the other type has a definite relation to the new formation of islands in the adult pancreas. The fact that islands entirely separated from the rest of the pancreatic tissue do exist under normal pathologic conditions may be regarded as morphologic evidence of an internal secretory activity of the islands. They cannot be accepted, however, as constituting an organ *sui generis*, since normally most of the islands are connected with acini which are capable of changing into island cells. The new formation of islands in adult pancreas may occur by transformation and hyperplasia of the acinar, centroacinar or duct cells. The article is copiously illustrated with photomicrographs.—J. P. S.

Diabetes complicating acromegaly and pituitrin-insulin antagonism. Wemyss (H. L.), *Edinburgh M. J.*, 1927, 34, 343-346.

This is a case report. Insulin injections lowered the blood sugar but when insulin and pituitrin were used the sugar level was not reduced.—J. C. D.

Growth of the thorax, heart, lungs and thymus in swine (Über das Wachstum des Brustkorbes und der Brustorgane (Herz, Lunge,

Thymus) während der Entwicklung beim Schweine). Lenkeit (W.), Ztschr. f. Anat. u. Entwicklungsgesch. (Berl.), 1927, 82, 603-642.

One hundred and twenty-one animals from the 4th to the 16th week were investigated biometrically. The report is largely of morphological interest.—A. T. R.

Iodin as a therapeutic aid to surgery in primary hyperthyroidism. Clute (H. M.), & Mason (R. L.), Boston M. & S. J., 1927, 197, 247-254.

The authors conclude from a study of their cases: that iodine is the important factor, for they got as good pre-operative results with hydriodic acid saturated with iodine as with Lugol's solution; that an excess of iodine is better than continued smaller doses; that iodine therapy should continue three months after operation; that some recurrences may be controlled with iodine, though as a rule further excision is indicated; that iodine is not a cure for exophthalmic goitre; and that iodine may be cautiously tried in pre-operative treatment of patients having multiple adenomatous goitres with hyperthyroidism.—J. C. D.

Management of the hypothyroid patient. Higgins (W. H.), South. M. J. (Birmingham), 1927, 20, 779-782.

The author emphasizes the observation of the basal metabolism, as indicating the effectiveness of the treatment and the need of correcting co-existing pathological conditions.

Toxic goiter. McClure (R. D.), & McGraw (A. B.), Ann. Clin. Med. (Balt.), 1927, 5, 626-634.

The authors have drawn upon their experience with a series of 211 cases, operated upon in 1925, to assemble their current views on the management of patients suffering from so-called toxic goiter. They bring out statistically that the degree of toxicity varies much more strikingly with the type of goiter encountered than with the age at which the goiter or its toxic symptoms made their appearance. They advocate the closest possible co-operation between surgeon and internist during the entire time the patient is under observation. They feel that adenomatous goiters should be excised, whether toxic or not, as a safeguard against future trouble. They discuss the relation of such associated complications as myocarditis, with or without auricular fibrillation, and diabetes mellitus to the

operability of cases with hyperthyroidism and reach the conclusion that these two complications are rarely if ever a barrier to successful operation if conducted with sufficient caution. In outlining pre-operative measures, they stress complete rest in bed, the use of iodine (Lugol's solution) in moderate doses, high fluid and food intake, and the use of mild sedatives, such as luminal. Post-operative treatment is likewise outlined emphasizing the maintenance of a large fluid and sugar intake immediately after operation by means of hypodermoclysis, proctoclysis, and intravenous medication if necessary. They stress the necessity of frequent follow-up visits during the first six months after operation in order to curtail the patients' activities and to detect promptly any signs of persistent or recurrent hyperthyroidism.—Authors' Abst.

Annual Index

Authors

- Abel, J. J. (Geiling, Rouiller, Bell and Wintersteiner): Crystalline insulin 363
- Adamberg, L.: cf. Lipschutz... 478
- Adlersberg, D. (Perutz): Increased regeneration of skin due to insulin..... 482
- Ainslee, Harriet B.: cf. Mochlig. 248
- Alexander, E. G.: Surgery in diabetes 71
- Allen, F. M.: Myrtillin..... 482
- Allen, F. N.: cf. Wilder..... 486
- Allen, R. E.: cf. Shepardson... 160
- Althausen, T. L. (Kerr): Hemochromatosis. A report of three cases with results of insulin therapy 377
- Altmann, F.: Cyclic changes in the ovary of the mole..... 602
- Aoki, K.: Reciprocal action of insulin and adrenalin on nitrogen metabolism 483
- Appel, K. E. (Cooper): Diabetic acidosis with negative ferric-chloride reaction in urine... 249
- Aron, M.: Development of foetal thyroid and pancreatic islets.. 84
- Ascheim, S.: cf. Zondek..... 246
- Asdell, S. A. (Marshall): Effect of ovarian hormone in producing pro-oestrous development in the dog and rabbit. 475
- Assimoff, G.: Biological control of antithyroidin 84
- cf. Zavadovsky 376
- Aszodi, Z. (Ernst): Action of pancreas extirpation followed by thyroidectomy on sensitivity of dogs to insulin..... 71
- Aub, J. C.: Relation of thyroid to calcium metabolism..... 491
- Aubertine, E.: Insulin..... 36
- Auger, L.: cf. Jung..... 254
- Backlin, E.: Epinephrine and blood pressure in dementia praecox and manic-depressive insanity 37
- Ballmann, E.: Acromicria..... 604
- (Hock): Anthropometric analysis of growth disturbances in hypophyseal diseases 65
- Baloget, L.: Testicular grafts in young goats 475
- Banting, F. G. (Gairns): Suprarenal insufficiency 37
- Barbour, A. D. (Chalkoff, Macleod and Orr): Influence of insulin on liver and muscle glycogen in the rat under varying nutritional conditions.... 250
- Barksdale, E. H.: Effect of lowering blood pressure on myocarditis caused by epinephrine hydrochloride and caffeine in rabbit 597
- Bartlett, William: The surgical treatment of goiter. (Book Review) 34
- Baumann, E. J. (Kurland): Changes in inorganic constituents of blood in suprarenal-ectomized cats and rabbits.... 149
- Bayer, G. (von den Velden): Klinisches, Lehrbuch der Inkretologie und Inkretotherapie. Book Review..... 848
- Beck, Harvey G.: The association of urologic lesions with hypothyroidism 438
- Bell, T. K.: cf. Abel..... 363
- Bellerby, C. W.: cf. Parkes.... 62, 152, 603
- Benatti, D.: cf. Rosello..... 47
- Berblinger, W.: Relation of facial hirsutism in women to the gonads, suprarenals and hypophysis 50
- Bergey, D. H.: Diabetes mellitus, etiology of..... 72
- Berliner, F.: cf. Hoag..... 488
- Bernstein, M.: Acromegaly.... 65
- Bertolani De Rio (Maria): Researches on sexual hormones. 57
- Bisceglie, V.: Action of splenic extracts on the blood corpuscles 82
- Blalock, A. (Harrison): Effect of thyroidectomy and thyroid feeding on cardiac output... 370
- Blatt, M. L. (Greengard): Diabetes insipidus 480
- Boivin, A.: Chemical composition of insulin, sulfur compounds 363

- Bonilla, E.: Dermatoses and glands of internal secretion... 50
- Hypophyseal obesity of syphilitic origin 65
- The syndrome of Block..... 57
- Thymic death 423
- Boukalik, W. F. (Hoskins): Further studies on testicular grafting 335
- Boyd, E.: Growth of thymus—its relation to status thymicolymphaticus and thymic symptoms 490
- Boyd, J. D.: cf. Hines..... 361
- Brain, W. R.: Heredity in simple goitre 371
- Bram, I.: Psychic trauma in pathogenesis of exophthalmic goiter 106
- Brambell, F. W. R. (Parks and Fielding): Changes in the ovary of mouse following X-rays 79
- Brand, E.: cf. Sandberg..... 79
- Britton, S. W. (Geiling): Medulladrenal secretion and carbohydrate metabolism 463
- cf. Geiling 484
- Brodd, C. A.: Creatine, creatinine and arginine in adrenalin action 241
- Brougher, J. C.: Blood calcium as affected by insulin..... 251
- Brouha, L. (Simonnet): Action of follicular fluid on uterine contractility 602
- — Effect of washing with physiological saline on spontaneous rhythm of uterus 476
- — Hypophysis and internal secretion of the ovary..... 480
- — Uterine contractility, oestrous and folliculine.... 476
- Browder, E. J.: cf. Gordon.... 265
- Brown, A.: cf. Morgan..... 82
- Buchbinder, W. C. (Kern): Calcium deficiency and bone changes in experimental obstructive jaundice 487
- Burge, W. E. (Estes, Wickwire, and Williams): Effect of internal secretions and temperature on metabolism of amino acids and simple sugars by animal cells 472
- (Williams): Utilization of dextrose, levulose and galactose in animal and plant cells, and antagonistic action of insulin to thyroxine. 483
- Burget, G. E. (Viesscher): Variations of pH of the blood and the response of the vascular system to adrenalin..... 351
- Burnett, T. C.: Further observations on the depressor substance in liver extract..... 338
- Byron, C. S.: cf. Collens..... 38
- Calvanico, R.: Histological modification in ovarian grafts.... 244
- Cameron, A. T. (Carmichael): An attempt to evaluate thyroid preparations, utilizing their effect on growth-rate and production of organ-hypertrophy in young white rats..... 85
- — Sudden atmospheric changes as contributory factors in the production of tetany 85
- (Foster): Contract of Chloride contents of corpuscles and plasma in pernicious anaemia and various other conditions 363
- (Kitchen and McRae): Physiological examination and basal metabolism of young adults 86
- cf. Ingvaldsen 88
- Cambridge, P. J. (Howard): Interrelation of insulin and other gland extracts in metabolism. 51
- Campbell, W. R.: Acidosis, coma and infections in diabetes-mellitus 72
- (Markowitz): Metabolism of dihydroxyacetone in pancreatic diabetes 251
- — Preferential utilization of carbohydrate in diabetes 607
- Cantarow, A.: cf. Gordon..... 157
- Carbohydrate retention in hypertension 260
- Carlson, A. J.: cf. Hektoen.... 493
- Carmichael, J.: cf. Cameron... 85
- Caskey, M. W. (Hamel): Effect of adrenalin on the temperature of skeletal muscle after stopping both venous and arterial blood flow through liver. 464
- Cassidy, G. J.: cf. Finney.... 252
- Castaldi, L.: Influence of adrenal cortex on body growth..... 241
- Castex, M. R. (Scheingart): Action of pituitary extract on metabolism 246
- Caven, W. R.: cf. Taylor..... 470

- Chabanier, H. (Lebert and Lobo-Onell): Rolé of purification of insulin preparations in hypoglycemia 483
- (Lebert, Lobo-Onell and Lumiere): Treatment of diabetic coma 154
- — — — Surgery, diabetes and insulin 250
- Chaikoff, I. L.: cf. Barbour... 250
- Chandler, S. B.: Healing of fractures in parathyroidectomized albino rats..... 369
- Relation of parathyroidectomy to pregnancy, lactation and growth of offspring in albino rats..... 369
- Chang, H. C. (Sloan): Influence of experimental hypothyroidism upon gastric secretion... 261
- Charles, J. R.: Manganese toxæmia and liver feeding..... 363
- Chase, Lillian A.: Diabetic lipæmia retinalis..... 364
- Hereditary diabetes insipidus. 359
- Chetivismus, S.: Treatment of infantilism 51
- Chydenius, J. J.: Structure of cells of human corpus luteum and its changes during cycle of menstruation and pregnancy 357
- Cipra, Anna: cf. Marine..... 263
- Clark, G. A.: cf. Eaves..... 247
- Clutet, H. M. (Mason): Iodin as therapeutic aid to surgery in primary hyperthyroidism.. 610
- Collens, W. S. (Shelling and Byron): Effect of adrenalin upon blood sugar following ligation of hepatic artery..... 38
- Collier, F. A. (Huggins): Tuberculosis of thyroid..... 371
- Collin, R.: Hypophyseal colloid and cerebro-spinal fluid 247
- Collip, J. B.: Animal passage hypoglycæmia 364
- Internal secretion of the parathyroid glands 79
- Colwell, A. R.: Relation of hypophysis to diabetes mellitus. 605
- Comas: cf. Marañon..... 47
- Cook, F.: cf. Jung..... 369
- Cooper, D. A.: cf. Appel..... 249
- Corey, E. L.: Effect of forcing fluids upon survival after bilateral epinephrectomy..... 38
- Cori, C. F. (Cori): Carbohydrate metabolism of adrenalectomized rats 597
- Cori, Gerty T.: cf. Cori..... 597
- Correa, L. M.: cf. Roffo..... 259
- Corscaden, J. A.: cf. Sharlit... 63
- Coulaud, E.: cf. Messerli..... 159
- Courrier, R.: Castration in bats. 244
- Quantitative action of follicular hormone 357
- (Potvin): Uterine reaction to injection of liquor folliculi in castrated rabbits. 357
- Covell, W. P.: Quantitative study of hypophysis of human anencephalic fetus..... 606
- Cramer, W.: Fever, infections and the thyroid-adrenal apparatus 371
- (Ludford): Cellular activity and cellular structure in thyroid gland 371
- cf. Ludford 367
- Crivellari, C. A.: Sensitiveness of adrenalectomized rats to certain toxic substances 464
- Csepai, K. (Weiss): Pituitrin sensitivity of human organism 66
- Curtis, A. N.: cf. Knowlton... 606
- Cushing, H. (Davidoff): Studies in acromegaly. IV. Basal metabolism 360
- Danenkiff, J. S.: cf. Sacharoff.. 368
- Darnet, J. J.: Insulin in dermatology 364
- Davidoff, L. M.: cf. Cushing... 360
- Davidson, E. C.: cf. Foster... 364
- Davies, D. T. (Dickens and Dodd): Preparation, properties and source of parathyroid hormone 488
- Davis, A. H. (Pack): Interstitial cells of Leydig in hermaphrodite pig 313
- Day, C. S.: cf. Ladd..... 485
- De Jong, D.: "Synthalin"..... 252
- De Lucas, C.: Clinical value of adrenalin in thyroid conditions 86
- De Paoli, M.: cf. Pighini..... 56
- Depisch, F.: Tolerance to different foods in diabetes 252
- (Hölger): Diabetes insipidus. 247
- Deulofeu, V.: cf. Pico..... 242
- Deutch, M.: cf. Marine..... 263
- Dickens, F.: cf. Davies..... 488
- Dietrich, S. (Loewi): Experiments on diabetes and insulin action 73
- Di Mattei, P.: Expansion of frog melanophores as a biologic test of hypophyseal extracts and influence of chloretone on test 481

Divorkin, S.: cf. Finney.....	252	Fishbaugh, Ernest C.: Head- ache in relation to ovarian dysfunction	445
Dodd, E. C.: cf. Davies.....	488	Fisher, N. F.: cf. Larson.....	233
Doisy, C. N.: cf. Jordan.....	59	Fitz, R.: cf. Murphey.....	249
Draper, W. B.: Unity of multi- plicity of autacoids of poste- rior lobe of pituitary gland...	152	Fitzgerald, R. R.: System of microscopic tubules in thyroid gland	372
Drury, D.: Otosclerosis.....	52	Fleischmann, W.: Influence of thyroid hormone on phagocy- tosis	87
Dulaney, H.: cf. Gibson.....	341	Flint, K. W.: cf. Ponder.....	92
Duncan, G. G.: (Frost): Prep- aration and management of surgical diabetic.....	73	Flynn, J. B.: cf. Yocom.....	593
Dworkin, S. (Finney): Artifi- cial hibernation in the wood- chuck	155	Foldes, E.: Effect of oral ad- ministration of sulphur on dia- betic metabolism	484
Eaves, E. C. (Clark): Changes in pituitary after section of right vagus	247	Foster, D. P. (Davidson): In- fluence of insulin on treatment of surgical complications in diabetes mellitus	364
Eggert, B.: Cyclic changes in Bidder's organ and gonads of the toad	58	Foster, G. L.: Tissue respira- tion in relation to thyroidec- tomy	87
Eisenman, Anna J.: cf. Swingle.	49	— (Smith): Hypophsectomy and replacement therapy	66
Elkourie, L. A.: cf. Larson....	489	Foster, Marion E.: cf. Cameron.	363
Engle, E. T.: cf. Smith.....	362	Frank, E. (Haring and Kühnau): Blood chemistry in parathy- reoprival tetany	80
Ernst, Z.: cf. Aszodi.....	71	— (Nothmann and Wagner): Synthalin—substitute for insulin for oral medication.	607
Estes, A. M.: cf. Burge.....	472	French, G. H.: A note on the parathyroid and broken bones	25
Evans, H. M.: Experimental gi- gantism—differential effect of anterior hypophyseal extract on normal and gonadectomized males and females.....	360	Fricke, G.: Glycosuria after in- sulin	253
Evans, J. I.: cf. Hartman.....	464	Fried, E.: cf. Frisch.....	149
Escudero, Pedro: Latent dia- betes	27	Frisch, F. (Fried): Blood cal- cium and adrenalin action....	149
Fahrni, G. S.: Surgical treat- ment of goitre	86	Fujii, M.: Action of cortical ex- tract of suprarenal	39
Falco, G.: Anatomical altera- tions in the experimental co- caine poisoning with particu- lar regard to the endocrine glands	53	Funk, C.: Rôle of vitamins and insulin in nutrition.....	608
Falta, Wilhelm: Erkrankungen der Blutdrüse (Book Review).	462	Gairns, S.: cf. Banting.....	37
Falta, W. (Högler): Water me- tabolism in myxedema and exophthalmic goiter.....	261	Galant, J. S.: Eunuchoidismus mulierum versus connatus....	58
Fels, E.: Ovarian hormone in blood	150	Gans, H. M.: Effect of early castration on voluntary activ- ity of male albino rats.....	141
Ferreira de Mira, M.: New re- search on action of extracts of adrenal gland on muscular fatigue	149	— Effect of fractional castra- tion on the voluntary activ- ity of male albino rats....	145
Fielding, U.: cf. Brambell.....	475	Gardiner-Hill, H. (Smith): Ef- fects of feeding anterior lobe pituitary extract to children..	606
Finney, W. H.: cf. Dworkin...	155	Geiger, E. (Szirtes): Maximum hypoglucemia without use of insulin	253
— (Dworkin and Cassidy): Ef- fects of lowered body tem- perature and of insulin on respiratory quotient of dogs	252		

Gelling, E. M. K. (Britton): Adrenal mechanism and modification of insulin action by post-pituitary extracts	484
— cf. Britton	463
Ghrist, D. G. (Rowntree): Addison's disease without pigmentation: Report of a case.	589
Greengard, J.: cf. Blatt	480
Geyelin, H. R.: Diabetes in children	73
Gibson, G. A.: Action of adrenalin in aplastic anemia	39
Gibson, R. B. (Magers and Dulaney): Blood sugar curves in diabetes insipidus and in habitual and experimental excessive water drinking	341
Glaser, E. (Halpern): Activation of insulin	155
Glaser, M.: Thyroxin and growth of white mice	87
Gley, P.: Functions of the adrenals	39
Glimm, E. (Wadehn): Sex hormone from placenta ("feminin")	245
Goldschmidt, S.: Function of the thymus gland	83
Goldstein, E. (Harris): Xanthoma diabetorum: Unusual process of involution	253
Goodale, H. D.: cf. Nonidez	159
Gordon, B. (Cantarow): Use of parathyroid extract in hemorrhage	157
Gordon, M. B. (Browder): Suprarenal carcinoma with pubertas praecox in a boy three years of age	265
Gray, S. H. (Haven and Loeb): Effect of potassium iodide and thyroid extract on thyroid gland of guinea-pig	261
Greenwald, I. (Gross): Effect of long continued administration of parathyroid extract upon excretion of phosphorous and calcium	80
Groedel, F. M. (Hubert): Diagnosis of disturbed thyroid function by interferometric test	87
Gross, J.: cf. Greenwald	80
Guerra, H.: Effect of pancreatic extract upon cardiac contraction	74
Guizzetti, P.: Structure of pars intermedia of hypophysis in man	153
Gunn, F. D.: cf. Hartman	351
Gunnar, B. (Ohlin): Pituitrin and blood lipoids	360
Haberlandt, L.: Hormone of heart movement	65
— Hormone sterilization of female animals. III. Feeding experiments with ovarian and placental optones.	358
Hahn, L.: Insulin and arterial blood pressure	74
Halpern, G.: cf. Glaser	155
Hammar, J. Aug.: On the asserted non-existence of the age of involution of the thymus...	18
Hammett, F. S. Cyclic character of response to parathyroid deficiency	493
— Rôle of thyroid and parathyroid glands in growth of central nervous system. Rôle of thyroid apparatus in solids—water differentiation of central nervous system during growth	492
— Studies of the thyroid apparatus. XLVIII. Age, sex, weight and season as lethal factors in conditions of parathyroid and thyroid deficiency	117
— Studies of the thyroid apparatus. XLIX. Water balance in conditions of thyroid and parathyroid deficiency	297
Hannan, J. H.: The flushings of the menopause. (Book Review)	461
Haring, W.: cf. Frank	80
Hartman, F. A. (Evans and Walker): Effects of epinephrin and of sympathetic stimulation upon skeletal muscle ..	464
— (MacArthur, Gunn, Hartman and Macdonald): Kidney function in adrenal insufficiency	351
Hartman, W. E.: cf. Hartman, F. A.	351
Hartmann, M.: Ovarian hormone	245
Harris, J.: cf. Goldstein	253
Harrison, G. A.: Insulin by injection a failure	364
Harvey, J. M. D.: cf. Olmstead.	258
Häusler, H. (Högler): Diabetes refractory to insulin	608
— (Loewi): Experiments on diabetes and insulin	74
Haven, F. L.: cf. Gray	261

Hektoen, L. (Carlson and Schulhof): Further attempts to experimentally increase hormone output by thyroid.....	493	Hölger, F.: cf. Depisch.....	247
Herlitz, C. W.: Hypoglycemia in children	365	— cf. Falta.....	261
Hermann, H.: Effects of injections of secretion.....	40	— cf. Häusler	608
Herschmann, H. (Neurath): Precocity of endocrine origin....	151	Holzbach, E.: Blood sugar in diabetes in pregnancy.....	74
Hertzler, A. E.: Pathology of goiter	582	Holzer, H. (Klein): Insulin treatment	155
Herxheimer, G.: Islands of Langerhans and insulin after ligation of veins that lead from pancreas	365	— cf. Klein	256
Hersfeld, E. (Mosler): Effect of pilocarpine on electrocardiogram in normal, in thyroid tested; and in thyroidectomized guinea pigs and rabbits.....	87	Hoskins, R. G.: Studies on vigor. XVI. Endocrine factors in vigor	97
Herzog, I.: Neural progressive muscular atrophy and disorders of inner secretions.....	58	— Thyroid administration in senility	136
Hevn, A.: Influence of ovarian function on basal metabolism.	476	— cf. Boukalik	335
Hickel, P. (Nordmann): Origin of the islands of Langerhans from excretory system of pancreas	485	Houssav, B. A. (Lewis and Molinelli): Influence of insulin upon secretion of adrenalin..	40
Hicks, C. S.: Innervation and secretory path of thyroid gland	262	— (Molinelli): Anaphylaxis and adrenalin discharge	45
Higgins, C. C.: Tuberculosis of thyroid gland	88	— — Blood supply and weight of adrenal glands and their relation to body surface and body weight.	150
Higgins, W. H.: Management of hypothyroid patient	611	— — Concentrated salt solutions causing adrenal discharge	45
Hilgartner, H. L. (Lankford): Retinitis pigmentosa arrested by ornanotherapy and anti-syphilitic treatment.....	237	— — Discharge of adrenaline produced by muscular activity	43
Hines, H. M. (Leese): Influence of pituitrin upon certain phases of carbohydrate metabolism	66	— — Discharge of adrenal by injection of various substances in the suprarenal	44
— (Leese and Boyd): Effect of pituitrin administration upon certain phases of carbohydrate metabolism.....	361	— — Hypothalamic center for adrenal secretion	44
Hirase, K.: Influence of extirpation of adrenals on work-capacity of muscle	40	— — Influence of yohimbine on splanchnic nerve action and of nicotine on adrenal secretion	149
Hirsch, M.: Handbuch der inneren Sekretion. (Book Review)	349	— — Liberation of adrenalin by puncturing or electrically exciting the medulla	41
Hoag, L. A. (Rivkin, Weigle and Berliner): Effect of potent parathyroid extract on calcium balance in infants....	488	— — Reflex secretion of adrenalin	42, 43
Hock, J.: cf. Ballman, E.....	65	Howard, H. A. H.: cf. Cambridge	51
		Howe, H. S. (McKinley): Cerebral circulation	465
		Hubert, G.: cf. Groedel.....	87
		Huggins, C. B.: cf. Collier.....	371
		Humel, E. J.: cf. Caskey.....	464
		Hunter, W. C. (Rush): Amyloidosis of the adrenals as a cause of Addison's disease....	45
		Husik, D. N.: Thymic death during tonsillectomy under local anesthesia	83
		Illievitz, A. B.: Observations on characteristics of urine in diabetes insipidus	361

- Ingvaldsen, T. (Cameron): Iodine compounds of thyroid... 88
- Irmie, C. G.: cf. Tingle... 248
- Ivy, A. C. (Oldberg): Adrenal auto-transplantation 465
- Iwanoff, G.: Anatomy and histology of interrenal bodies of man 598
- Izawa, Y.: Removal of pineal from both sexes of immature albino rats 82
- Jaffe, H. L.: Transplantation of guinea pig suprarenal and functioning of grafts 352
- Jaffe, R. H.: Histological and microchemical studies on lipin content of human thyroid.... 89
- Jamieson, H. C.: Diabetes mellitus and myxoedema 89
- Jennings, A. F. (Wallace): The field of usefulness of iodine in goitre 431
- John, Henry J.: Carbohydrate metabolism in hyperthyroidism 497
- Diabetes. One thousand cases. 156
- Hyperinsulinism 75
- Relationship of obesity to carbohydrate metabolism 366
- Technique in management of diabetic patients 35
- John, W. S. (O'Mulvenny, Potts and Laughton): Studies on anterior lobe of pituitary body 153, 247
- Jones, J. H.: Effect of administration of cod liver oil upon thyroparathyroid-ectomized dogs 262
- Jordan, C. N. (Doisy): Effect of light upon follicular hormone 59
- Jordan, E. M.: Effect of injected glucose on tolerance... 254
- Jorns: Endocrine pancreas function after ligation of ducts. 254
- Jung, F. T.: Existence of a parathyroid hormone 489
- (Cook): Effect of magnesium sulphate on parathyroidectomized rats 369
- Jung, L. (Auger): Insulin, arterial tension and glucemia... 254
- Junkersdorf, P. (Schüler): Action of adrenalin in association with complete diet 352
- Kallner, A.: cf. Rosenberg... 259
- Karplus, J. P. (Kreidl): Relation of hypothalamus centers to blood pressure and internal secretion 355
- Katayama, I.: Diagnostic value of the Kottman reaction in thyroid dysfunction 262
- Katsura, S. (Kozuka): Influence of pancreatic hormone on lymph 254
- Kauffmann-Cosla, O. (Roche): Action of insulin on disappearance of glucose and oxidations in blood in vitro 75
- (Zorkendorfer): Action of Marienbad mineral water on respiratory quotient and metabolism of phosphorus in diabetic 255
- Kaufmann, Margot: Effect upon intestine of extract of posterior lobe of hypophysis..... 248
- Kelly, T. C.: cf. Sturdevant... 472
- Kepinow, L. (Lebert): Rapid disappearance from blood of insulin injected intravenously. 255
- Kerley, C. G.: Hypopituitarism; congenital pituitary tumor; optic nerve atrophy..... 481
- Kern, Ruth: cf. Buchbinder... 487
- Kerr, W. J.: cf. Althausen... 377
- Kiehl, W. D.: Goitre from standpoint of prevention..... 89
- Killian, J. A.: Antiketogenic influence of insulin in diabetes mellitus 255
- King, Helen D.: cf. Loeb... 600
- King, Jessie L.: Menstrual records and vaginal smears in a selected group of normal women. 358
- Kitchen, H. D.: cf. Cameron... 86
- Klein, I. (Rischawy): Insulin and diuresis 255
- Klein, O.: Insulin hypoglycemia in man 366
- (Holzer): Insulin in hepatic diseases 256
- cf. Holzer 155
- Knaus, H. H.: Action of pituitary upon pregnant uterus of rabbit 66
- Knowlton, F. P. (Curtis and Silverman): Influence of pituitrin on diuresis variously induced. 606
- Kohn, A.: Structure of the embryonal ovary of the horse with special reference to the interstitial cells 59
- Kohno, S.: Comparative histology and embryology of the adrenals of mammals and man 46
- Kolliner, Martha: Influence of different diets on the nucleoplasma ratio of cells in adrenals of rat..... 598

- Koppányi, T.: cf. Luckhardt... 466
- Korenchevsky, V.: Influence of glycerine emulsion of testes and adrenals on tuberculous and senile patients..... 53
- Influence of injections of emulsions of testes and prostate and of insulin-like substances upon nitrogen metabolism of normal, castrated and thyroidectomized rabbits 59
- Influence of injections of testicular or ovarian emulsions upon nitrogen and gaseous metabolism of dogs and rabbits 60
- Influence of removal of thyroid, parathyroid and sexual glands and of thyroid feeding upon regulation of body temperature of rabbits.... 53
- Kozuka, K.: cf. Katsura..... 254
- Kraft, A.: cf. Van Dyke..... 481
- Kreitmair, H.: Pharmacological effect of ephedrine..... 241
- Krizenecky, J. (Podhrasky): Influence of hypophysis on growth and development 67
- Krizenencky, J. (Podhradsky): Antagonism of thyroid and thymus 491
- Kühl, G.: Experiments on hormone action of adrenal cortex 46
- Kühnau, J.: cf. Frank..... 80
- Kurland, S.: cf. Baumann..... 149
- Kurokawa, T.: Ability of tissue cells to take up and fix sugar. 256
- Kyrklund, K.: Combined skull necrosis, exophthalmos, Fröhlich syndrome and diabetes insipidus 54
- La Barre, J.: cf. Zunz.... 260. 355
- La Barre, Jean: Existence of a physiologic insulinemia..... 257
- Increase in insulin content of pancreatic venous blood after excitation of vagus nerve 256
- Ladd, W. S. (Day): Growth in children with diabetes mellitus 485
- Lanczos, A.: cf. Mansfeld..... 263
- Landsberg, M.: Clinical study of substance A isolated from insulin 609
- Langeron (L.) et al.: Tetany and syphilis of the parathyroids 158
- Lankford, J. S.: cf. Hilgartner. 237
- Laqueur, E.: Female sex hormone, menoformon 602
- Larson, E. (Elkourie): Rôle of toxins in parathyroid tetany.. 489
- (Fisher): Effect of pregnancy and lactation on the blood calcium of thyroparathyroidectomized dogs 233
- Laubmann, W.: Development of the hypophysis in hypogeophis rostratus 68
- Laughton, N. B.: cf. Johns. 153, 247
- Lawrence, C. H.: Physiological background for symptoms of thyroid failure, with consideration of results of treatment 89
- The effect of thyroid extract upon bodily function in hypothyroidism 321
- Lawrence, R. D.: Action of insulin in glycogen formation and its therapeutic application 257
- Best time for blood sugar tests in diagnosis and treatment of diabetes 366
- Lebert: cf. Chabanier. 154, 250, 483
- cf. Kepinow 255
- Lee, M. O.: Basal metabolism in rat during oestrous cycle.... 478
- Leese, C. E.: cf. Hines..... 66, 361
- Lieberfarb, A. S.: Movements of empty crop of fowl in acute hyperthyroidism 372
- Lenkeit, W.: Growth of thorax, heart, lungs and thymus in swine 610
- Leulier, A.: cf. Mouriquand. 242, 468
- Levinson, S. A. (Matthews): Parathyroid hypercalcemia and anaphylactic shock 81
- Lewis, J. T. (Torino): Sensitiveness of suprarenalectomized rats to morphine..... 494
- cf. Houssay 40
- cf. Torino 471
- Lin, K. H.: cf. Shen..... 359
- Lindsey, Blanche (Medes): Histological changes in testis of guinea pig during scurvy and inanition 245
- Lipschutz, A. (Vesnjakov, Tuisk and Adamberg): Attempt to purify a morphogenetic..... 478
- Lisser, H. (Smith and Shepardson): Maternal tetany relieved by parathyroid extract-Collip. 81
- Lobo-Onell: cf. Chabanier..... 154, 250, 483
- Loeb, Leo.: cf. Gray..... 261

- Loeb, L.: Syngenesiotransplantation in the guinea pig.....600
 — Syngenesiotransplantation in the rat601
 — (King): Transplantation and individuality differential in strains of inbred rats.....600
 Loeper, M. (Ollivier): Lipoid metamorphosis of two suprarenal glands with melanoderma.352
 Loewe, S.: Emmenagogue action of ovarian hormone.....245
 — (Voss and Paas): Female sexual hormones 61
 Loewi, O.: cf. Dietrich..... 73
 — cf. Häusler 74
 Lopez, J. M.: Spectrophotometric study of adrenaline.....242
 Lopez, V. (Lucas): Three cases of pseudohermaphroditism.... 61
 — cf. Marañón 47
 Lublin, A.: Influence of insulin on utilization of carbohydrates by non-diabetic organism.....367
 Lucas, G. H. W.: Blood and urine findings in desuprarenalized dogs 37
 Lucas, S.: cf. Lopez..... 61
 Luckhardt, A. B. (Koppányi): Conditions under which hypodermically administered epinephrin gives pressor effect..466
 Ludford, R. J. (Cramer): Secretion and the Golgi apparatus in cells of islets of Langerhans367
 — cf. Cramer371
 Lumiere: cf. Chabanier...154, 250
 Lundberg, E.: Antagonism between thyroid and pancreas..372
 — Relation between internal secretion of thyroid and sex glands373
 Lyall, A.: Effect of protein in diet of patients suffering from diabetes mellitus367
 Lyle, W. G.: cf. Sharlit..... 63
 Lyon, D. M. (Redbead): Synthetic thyroxin—clinical tests.263
 MacArthur, C. G.: cf. Hartman.351
 Macdonald, J. J.: cf. Hartman.351
 Macleod, J. J. R.: cf. Barbour.250
 Magers, Elizabeth H.: cf. Gibson.341
 Mandl, F.: Osteitis fibrosa.....260
 Mansfeld, G. (Lanczos): Antemortem protein decomposition after thyroidectomy263
 Marañón, G.: Diabetes insipidus with great polyuria and probable tubercular lesion of posterior lobe of hypophysis..... 68
 Marañón, G.: Diagnosis and classification of forms of hypothyroidism 90
 — Endocrine or neurogenic origin of so-called hypophyseal obesity 68
 — The pancreatic-suprarenal antagonism in physiology and in the clinic 76
 — (Comas and Lopez): Case of sudden death of suprarenal origin not diagnosed..... 47
 Marine, D.: Calcification of suprarenal glands of cats.....353
 — (Baumann): Duration of life after suprarenalectomy in cats and attempts to prolong it by injections of solution containing sodium salts, glucose and glycerol.353
 — (Deutch and Cipra): Effect of ergotamine tartrate on the heat production of normal and thyroidectomized rabbits263
 — — — Effect of large doses of iodine on heat production in rabbits...263
 Markowitz, J. (Soskin): Pancreatic diabetes and pregnancy 76
 Marvel, L.: Sensibility of rats to cold after adrenalectomy..354
 Mason, E. H.: Pre-operative preparation of diabetic patient 76
 Mason, R. L.: cf. Clute.....610
 Markowitz, J.: cf. Campbell.251, 607
 Mathews, S. A.: cf. Levinson.. 81
 Maxenchs, A. T.: Study of epinephrine242
 McCarrison, R.: Goiter prevention159
 McClure, R. D. (McGraw): Toxic goiter611
 McGraw, A. B.: cf. McClure...611
 McKinley, E.: cf. Howe.....465
 McLean, S.: cf. Wallstein....491
 McRae, D. F.: cf. Cameron.... 86
 Meakins, J. C.: Reaction of chronic nephrosis to thyroid and parathyroid medication...494
 Medes, Grace: cf. Lindsay....245
 Medlar, E. M.: Report of two cases of adrenal insufficiency (Addison's disease)599
 Merriam, J. (Smith): Case of adrenal adenoma599
 Messerli, F. M. (Coulard): Changes in thymus and thyroid in endemic goiter.....159
 Michail, D. (Vancea): Action of insulin on naphthalinic cataract258

Michaux, A.: cf. Randoin.....	243
Michalescu: cf. Urechia.....	474
Mikami, S.: Effect of insulin upon carbon dioxide content in arterial blood sugar level in rabbits poisoned by carbon monoxide	258
Miley, H. H.: Effects of ovarian extirpation on fatigability of muscle in rat.....	476
Miller, E. A.: cf. Visscher.....	604
Miller, H. R.: Use of insulin by mouth	76
Mills, C. A.: cf. Shih-Hoa.....	78
Millzner, R. J.: Occurrence of parathyroids on anterior surface of thyroid gland.....	158
Mikulowski, V.: Disturbances of humoral equilibrium vascular-endocrino-automatic complex accompanied by cylindruria...	472
Moehlig, Robert C.: Vertigo and deafness associated with hypothyroidism	229
— (Ainslee): Pituitary gland and cholesterol metabolism.	248
— — Posterior pituitary extract and cholesterol metabolism	248
Molinelli, E. A.: Adrenaline function of adrenals in diphtheria poisoning	47
— Influence of normal adrenalin on arterial pressure and glucemia	467
— Influence of variation of arterial pressure due to bleeding or transfusion upon adrenalin secretion	467
— Splenic constriction caused by muscular metabolites. A double mechanism, nervous and adrenal.....	466
— cf. Houssay	40, 41, 42, 43, 44, 45, 149, 150
Moller, E.: Clinical investigation into the basal metabolism in diseases of the thyroid gland.	495
Monod, G.: Modern views on Vichy treatment of diabetes..	77
Monroe, R. T.: cf. Murphey...	249
Moore, C. R.: Qualitative indicator for testis hormone.....	603
— Testis graft reactions in different environments (rat).	477
Morelli, Elisa: Thyroid alterations in hereditary syphilis...	90
Morgan, E. A. (Rolph and Brown): Clinical manifestations of enlarged thymus....	82
Mori, K.: Influence of thyroid and insulin on oxydases in different organs	243
Mosler, E.: cf. Herzfeld.....	87
Mouriquand, G. (Leulier): Does adrenaline exist in a totally free state in fresh suprarenal capsules?	242
— (Leulier): Virtual adrenalin.	468
Muntwyler, E.: cf. Wenner....	261
Murlin, J. R.: Depancreatized dogs kept alive several months with insulin administered by stomach tube	609
Murphey, W. P. (Monroe and Fitz): Changes in composition of blood in pernicious anemia.	249
Nadler, J. E.: Quantitative comparison of epinephrin and ephedrin	354
Neurath, R.: cf. Herschmann..	151
Nishimura, H.: cf. Ogata.....	457
Noble, E.: Myxedema and myxedema therapy	494
Nonidez, J. F. (Goodale): Histologic studies on endocrines of chicks deprived of ultraviolet light	159
Nordmann, J.: cf. Hickel.....	485
Nothmann, M.: cf. Frank.....	607
Novak, Emil: How far can recent studies on the ovarian follicular substance be applied to the human? A brief discussion of the therapeutic aspects of the problem.....	173
Ogata, D. (Nishimura): New (orbital) method for extirpation of hypophysis in pigeon.....	457
Ohlin, C. A.: cf. Gunnar.....	360
O'Keefe, C. D.: Relation of hypothyroidism to obstetrics and gynecology	263
Oldberg, E.: cf. Ivy.....	465
Ollivier, J.: cf. Loeper.....	352
Olmstead, J. M. D. (Harvey): Glycogen content of frog's muscle after injection of insulin and its relation to contraction.	258
O'Mulvenny, O.: cf. Johns.....	153
O'Mulvenny, T. O.: cf. Johns..	247
Orr, M. D.: cf. Barbour.....	250
Oslund, R. M.: Cryptorchid testes and testicular hormone production	62
— Ligation of vasa efferentia in rats	62

Otani, S.: Studies on islands of Langerhans in human pancreas. I. Relation of islands to surrounding structures	609
— Studies on islands of Langerhans in human pancreas. II. Significance of variation in structure	610
Paas, Elizabeth: . cf. Loewe.....	61
Pack, G. T.: cf. Davis.....	313
de Paoli, M.: cf. Pighini.....	473
Pardo: cf. Soler.....	70
Parkes, A. S.: Occurrence of oestrous cycle after x-ray sterilization	479
— (Bellerby): Distribution in ovary of oestrous-producing hormone	62
— Effects of injection of oestrin during lactation....	152
— Significance of oestrin in placenta	603
— cf. Brambell	475
Paton, D. N. (Sharpe): Increase of methyl-guanidine in blood after parathyroidectomy	370
Peiper, H.: cf. Schmieden.....	243
Petren, Karl: Iodine and morbus Basedow (exophthalmic goiter)	1
Perutz, A.: cf. Adlersberg.....	482
Peynet, J.: cf. Sainton.....	374
Pico Estrada, O.: Blood sugar, glucose consumption and formation of glycogen after removal of suprarenals	150
Pico, O. M. (Deulofeu): Gases of blood in suprarenal insufficiency	242
Pighini, G.: Experimental researches on goiter-cretinism..	90
— (de Paoli): Endocrine glands of rats in parabiosis.....	473
— Relation between thyroid and cholesteroline and phosphate change in blood, adrenals, and sexual glands	56
Pilcher, J. D.: Relief of itching by epinephrin in infantile eczema,	468
Pitfield, R. L.: I. Production of mydrasis in white rabbits by injection of thyro-toxic blood serum and adrenaline. II. Detection of a toxic principle in the blood	91
Podhrasky, J.: cf. Krizenecky	67, 491
Poggio, G.: Basal metabolism in human diabetes.....	77
Pokorny, F.: Comparative anatomy of the hypophysis.....	69
Ponder, E.: Studies on Arneth Count. IV. Deflection by thyroïd injections	92
— (Flint): Studies on the Arneth Count. III. Effect of thyroidectomy	92
Popa, G. T.: A lipo-gel reaction exerted by follicular fluid upon spermatozoa and its significance	346
Potts, E. B.: cf. Johns....	153, 247
Potvin, R.: cf. Courrier.....	357
Power, M. H.: cf. Wilder.....	486
Pratt, J. P.: Corpus luteum in its relation to menstruation and pregnancy	195
— Internal secretion of ovary....	358
Priesel, R. (Wagner): Danger of insulin hypoglycemia in children	258
Quiñones, M.: Diabetes and its treatment	35
Raab, W.: Influence of central nervous system in disturbances of fat metabolism	69
Rabinowitch, I. M.: Cholesterol content of blood plasma as index of progress in insulin-treated diabetics	367
— Diabetic gangrene.....	78
— Insulin oedema	368
Rahlf's, S.: Dystrophia adiposogenitalis in three brothers....	607
Ramfrez, E.: Corpus luteum in hen and in mammals.....	246
Randoin, L. (Michaux): Comparative variations in content of suprarenals in water, fatty acids and cholesterol in normal pig	243
Ray, L. A.: cf. Robertson....	70
Redbead, F. A.: cf. Lyon.....	263
Richter, H. M.: Thyroidectomy: Its relation to cure of thyrotoxicosis	93
— (Zimmerman): Latent post-operative tetany.....	373
Richter, W.: Myxedema and exophthalmic goiter	94
Riddle, O.: Studies on thyroids..	161
Rinck, H.: Catabolism of sex glands in a case of pseudohermaphroditism	603
Rischaw, E.: cf. Klein.....	255
Rivkin, H.: cf. Hoag.....	488

- Robertson, H. E.: -cf. Wilder... 486
- Robertson, T. B. (Ray): Influence of tethelin upon growth and longevity of white mouse 70
- Roche, J.: cf. Kauffmann-Cosla 75
- Rochlin, D. G.: Pseudoepiphyses in endocrinology 601
- Rodriguez, E.: cf. Rossello.... 48
- Roffo, A. H. (Correa): Insulin-like substances in malignant tumors 259
- Rolph, A. H.: cf. Morgan..... 82
- Romeis, B.: Morphology of the parathyroid gland in Anura... 81
- Rosenberg, M. (Kallner): Glycemia and diseases of the stomach 259
- Rosendahl, G.: Diabetes mellitus and hypoglycemia..... 259
- Rosello, H. (Benatti): Compression of the suprarenal caps... 47
- (Rodriguez): Hypoglycaemia by adrenalin 48
- Rouiller, C. H.: cf. Abel..... 363
- Rowntree, L. G.: cf. Ghrist.... 589
- cf. Snell 193
- Rumph, P. (Smith): Occurrence of secretory products and specific structural differentiation in the thyroid and anterior pituitary during the development of pig foetus..... 496
- Rush, H. P.: cf. Hunter..... 45
- Sacharoff, G. P. (Danenkiff): Activity of insulin and dysfunction of endocrine glands.. 368
- Sacks, J.: Effect of adrenalin on phosphorous partition in muscle 468
- Sainton, P. (Peynet): Effect of experimental hyperthyroidism upon plumage 374
- Saito, S.: cf. Sugawara..... 469
- Sakamoto, S.: Castration and transplantation of testicles of fowl 358
- Saller, K.: Quantitative studies on the effects of inanition overfeeding and feeding thyroid gland on the testis..... 63
- Sandberg, Marta (Brand): Arginine and its possible relation to physiological activity of insulin 79
- Santenaise: Physiological ideas on vagotonia (pancrease and vagal tonus) 156
- Sataké, Y. (Sugawara and Watanabé): Method for collecting blood from suprarenal gland in dog, without fastening, narcotizing, laparotomy or provoking pain 468
- Schiroky, W. F.: cf. Smirnow... 354
- Schmieden, V. (Peiper): Diagnosis of primary suprarenal tumors 243
- Schou, H. I. (Susman): Endocrines in epilepsy: a histological study 355
- Schteingart, M.: cf. Castex.... 246
- Schulhof, R.: cf. Hektoen.... 493
- Schüler, H.: cf. Junkersdorf... 352
- Schütz, F.: Internal secretion and pregnancy 374
- Serdjukoff, M. G.: Ovarian heterografts in various endocrinopathies 64
- Serraller, F. E.: Cholesterol in diabetes and influence of insulin 78
- Shapiro, S.: Relation of certain glands of internal secretion to development of atherosclerosis 279
- Sharlit, H. (Corscaden and Lyle): Symptoms associated with menstrual cycle and effects thereon of ovarian therapy 63
- Sharpe, J. S.: cf. Paton..... 370
- Shelling, D. H.: cf. Collens.... 38
- Shen, T. C. (Lin): Nitrogen metabolism of eunuchs 359
- Shepardson, H. C. (Allen): Treatment of obstinate obesity 160
- cf. Lisser 81
- Shih-Hao, L. (Mills): Effect of insulin on blood cholesterol, fat and sugar in nephrosis.... 78
- Silverman, A. C.: cf. Knowlton. 606
- Simonds, J. P.: Organization of experimental adrenal cell emboli in lungs..... 599
- Simonnet, H.: cf. Brouha.... 476, 480, 602
- Simpson, Ethel D.: Changes in growth of skeletal muscle following thyroidectomy in sheep 94
- Is thyroidectomy the primary cause of arrested development of skeletal muscle in cretin sheep?..... 364
- Simpson, Miriam E.: cf. Evans. 360
- Sloan, J. H.: cf. Chang..... 261
- Slonaker, J. R.: Effect of follicular hormone on old albino rats 479

- Smirnow, A. J. (Schiroky): Vagotropic influence of adrenalin354
- Smith, G. H.: Bactericidal action of serum following injections of adrenalin469
- Smith, J. F.: cf. Gardiner-Hill.606
- Smith, L. W.: cf. Merriam....599
- Smith, Margaret C.: Interruption of pregnancy in rat by injection of ovarian follicular extract 64
- Smith, P. E.: Experimental feeding of fresh anterior pituitary substance to hypophysectomized rat361
- Induction of precocious sexual maturity by pituitary homeotransplants154
- Genital system responses to daily pituitary transplants. 64
- (Engle): Induction of precocious sexual maturity in mouse by daily pituitary homeo- and hetero-transplants362
- cf. Foster..... 66
- Smith, R. N.: cf. Lisser..... 81
- Smith, R. P.: Diabetes in child three years of age.....368
- Snell, A. M. (Rowntree): Clinical manifestations of water intoxication in a case of severe diabetes insipidus, with some notes on the disturbances of blood composition and vasomotor mechanism209
- Soler, B.: Insulin in cardiac insufficiency in a pregnant diabetic with acidosis..... 78
- (Pardo): Hypophysis and diuresis 70
- Soskin, S.: cf. Markowitz..... 76
- Speidel, C. C.: Behavior of epidermal mitochondria and pigment in frog tadpoles under thyroid accelerated metamorphosis and regeneration after wound inflection374
- Bile pigment production and erythrocyte destruction in thyroid-treated amphibian larvae.374
- Sserdjukoff, M.: Incretory processes of ovary and adrenal cortex 56
- Straemmler, M.: Pituitary etiology of diabetes insipidus... 70
- Stanley, L. L.: Effects of testicular substance implantations on glycosuria305
- Starr, P.: The course of hyperthyroidism under iodine medication160
- Stefanescu, Marie: Effect of hypophyseal extract on bone development362
- Steppuhn, O. (Sargin): Influencing peripheral action of epinephrine by extracts of organs599
- Strong, R. M.: Observations on skeleton of progeny of parathyroidectomized albino rats..370
- Sturtevant, C. N. (Kelly): Neurocytoma of the left suprarenal gland with metastases to the liver, skull and bones.....472
- Sugawara, T. (Watanabe and Saito): Effect of stimulation of sensory nerves upon rate of liberation of epinephrin from suprarenal glands469
- cf. Satake468
- Sun, T. P.: Epinephrin content of suprarenals of thyroidless rats470
- Supniewski, J. V.: Influence of insulin on acetaldehyde formation in body of animals.....259
- Susman, W.: cf. Schou.....355
- Sutton, L. R.: Abnormal growth in a girl.....473
- Swingle, W. W.: Blood changes and acid-base equilibrium in epinephrectomized cats..... 48
- Blood changes following bilateral epinephrectomy in cats 48
- Effect upon amphibian differentiation of feeding iodo-fibrin, iodoedestin and iodogliadin 71
- (Eisenman): Acid-base equilibrium of epinephrectomized cats 49
- Szirtes, L.: cf. Geiger.....253
- Szman, J. G.: Effect of testis on metabolism in chicken....152
- Takechi, K.: Morphology of the suprarenal cortex after castration, experimental cryptorchidism and implantation of in guinea pigs..... 49
- Taussig, A. E.: Diabetes mellitus, refractory to insulin....486
- Taylor, N. B. (Caven): Observations upon serum calcium after adrenalectomy470
- Thoemes, F.: Sporadic cretinism.375

- Thorpe, E. S.: Unusual case of thymic hypertrophy491
- Tietze, K.: Relationship between thyroid secretion and the size of the spleen..... 95
- Tingle, C. D. (Irmie): Effect of pituitrin on blood sugar.....248
- Torino, A. (Lewis): Morphine intoxication in adrenalectomized rats471
- Troell, A.: Indications for thyroidectomy and late results from the operation.....376
- Tuisk, R.: cf. Lipschutz.....478
- Urechia (Mihalescu): Arteriosclerotic dementia with gynecomastia474
- Van Dyke, H. B. (Kraft): Rôle of hypophysis in initiation of labor481
- von den Velden, R.: cf. Bayer..848
- Verdozzi, C.: Lactation and the glands of internal secretion..480
- Verzar, F.: cf. Zih..... 96
- Vesnjakov, R.: cf. Lipschutz...478
- Viale, G.: Endocrine factors in oxalic acid metabolism.....260
- Vines, H. W. C.: Action of suprarenal tissue upon lecithin.224
- Action of ultra-violet light, thyroid and parathyroid substances upon an artificial plasma in vitro.....125
- Replacement of serum calcium in rabbits after intravenous injections of oxalate and thyroid gland.....290
- Visco, S.: Behavior of hepatic glycogen in fasting animals treated with insulin..... 79
- Visscher, M. B. (Miller): Influence of insulin upon mammalian heart604
- cf. Burget351
- Voss, H. E.: Physiology of rut guinea pigs359
- cf. Loewe..... 61
- van Wagenen, Gertrude: Weight and dimensional effects of anterior hypophyseal extract on gonadectomized male rat.....362
- Walker, H. G.: cf. Hartman...464
- Wallace, S. W.: cf. Jennings..431
- Wallstein, M. (McLean): Hodgkin's disease, primary in the thymus gland491
- Watanabé, M.: cf. Satake.....468
- cf. Sugawara469
- Weigle, C. E.: cf. Hoag.....488
- Weiler, E. S.: Rôle of carbohydrate retention in hypertension260
- Wegelin, C.: Pathologic anatomy of endemic goiter and control of goiter in Switzerland..... 95
- Weiser, W.: Roentgenotherapy in psychiatric and neurological diseases in childhood..... 56
- Weiss, I.: cf. Csepia..... 66
- Wemyss, H. L.: Diabetes complicating acromegaly and pituitrin-insulin antagonism610
- Wenner, W. F.: Prevention of tetany by oral administration of ammonium chloride 81
- Prevention of tetany by oral administration of magnesium lactate490
- (Muntwyler): Hydrogen ion concentration and carbon dioxide content of blood of parathyroidectomized dogs.261
- Whitehouse, B.: Problem of menstrual function with observations on relation of the Graafian follicle and corpus luteum to pathological uterine hemorrhage604
- Wickwire, G. C.: cf. Burge....472
- Wieser, W. F.: Therapeutic action of roentgen rays on endocrine glands355
- Wilder, R. M. (Allen, Power and Robertson): Carcinoma of the islands of the pancreas.....486
- Williams, Maude: cf. Burge.472, 483
- Winn, R. C.: Simplification of dietetic treatment of diabetes mellitus157
- Wintersteiner, O.: cf. Abel....363
- Wolf, H. J.: Influence of insulin and glucose on oxygen-use of surviving frog's spinal cord.368
- Wolfson, H.: Antagonistic action of internal secretions of pancreas and thyroid.....487
- Wagner, A.: cf. Frank.....607
- Wagner, R.: cf. Priesel.....258

- Yocom, H. B. (Flynn): Physiological castration in the fowl. 593
- Zavadovsky, B. (Asimoff): Fixing of thyroxine in organism of hyperthyroidized mammals... 376
- Zid, A. (Verzár): Action of thyroid secretion on gaseous metabolism in vitamin-B deficiency 96
- Zimmerman, L. M.: cf. Richter. 373
- Zondex, B. (Ascheim): Ovarian hormone and genitalia..... 246
- Zorkendorfer, W.: cf. Kauffmann-Cosla 255
- Zunz, E. (La Barre): Insulin content of pancreatic venous blood after hyperglucemia caused by injection of glucose. 260
- X-rays and adrenalin in blood 355
- Zwemer, R. L.: Prolongation of life after complete epinephrectomy 50

Subjects

Acromegaly, basal metabolism in.	360	Adrenal in diphtheria poisoning..	47
Acromicria, a case of.....	604	— — hemochromatosis	377
Addison's disease, amyloidosis of		— injection and emboli in lungs.	599
adrenals as a cause of.....	45	— insufficiency and kidney func-	
— — case reports of.....	599	tion	351
— — without pigmentation.....	589	— — case reports of.....	599
Adrenal	598	— — gases of the blood in....	242
— ablation, and sensitiveness to		— (left), neurocytoma of.....	472
certain toxic substances...	464	— lipoids	56
— — — serum calcium	470	— mechanism and modification	
— — — morphine	494	of insulin action by post-	
— — — intoxication	471	pituitary extracts	484
— — blood and urine after.....	37	— (medulla) ablation and car-	
— — prolongation of life after..	50	bohydrate metabolism	463
— action of cortical extract of..	39	— method of collecting blood	
— adenoma	599	from	468
— amyloidosis of, as a cause of		— of mammals and man, com-	
Addison's disease	45	parative histology and em-	
— and epilepsy	355	bryology of	46
— — lipid metamorphosis	352	— of rat, influence of diets on	
— — pancreatic extract	40	the nucleo-plasma ratio....	598
— — sudden death	47	— pancreatic antagonism	76
— — testes, influence of glycer-		— secretion and arterial pressure.	467
ine emulsions of, on tu-		— — hypothalamic center for... 44	
berculous and senile pa-		— — influence of yohimbine and	
tients	53	nicotine on	149
— — vigor	99	— thyroid apparatus, fever and	
— — work-capacity	40	infections	371
— auto-transplantation	465	— tissue, action of upon lecithin.	224
— blood supply and weight of,		— transplantation	352
and relation to body surface		— tumors	243
and weight	150	Adrenalectomy and blood sugar.	150
— calcification in cats.....	353	— — changes in inorganic con-	
— compression of, and discharge		stituents of blood.....	149
of adrenalin	47	— bilateral, effect of forcing liq-	
— content of in water, fatty acids		uids upon survival after....	38
and cholesterol	243	— glucose consumption and gly-	
— cortex and intravital staining	56	cogen formation	150
— — hormone	46	— and sensibility to cold.....	354
— — influence of, on body growth.	241	— in cats, blood changes follow-	
— discharge, caused by concen-		ing	48
trated salt solutions	45	— survival after, modified by so-	
— — — injections of sub-		dium salts, glucose and gly-	
stances into supra-		cerol	353
renal	44	Adrenalectomized cats, acid-base	
— — produced by muscular ac-		equilibrium of	49
tivity	43	Adrenalin action and blood cal-	
— extirpation and blood pressure.	355	cium	149
— — — carbohydrate metabo-		— — and diet	352
lism	597	— — of, in aplastic anemia....	39
— — blood changes and acid-base		— and bactericidal action of se-	
equilibrium after.....	48	rum	469
— extracts of, and muscular fa-		— — blood pressure in dementia	
tigue	149	praecox and manic-de-	
— functions of	39	pressive insanity	37
— hyperglycemia and myrtillin..	482	— — — sugar following ligation	
		of hepatic artery....	38

Adrenalin and cerebral circulation	465	Basal metabolism in rat during oestrous cycle.....	478
— fresh suprarenal capsules..	242	— of young adults.....	86
— hypoglycemia	48	Basedow's Disease, iodine and...	1
— infantile eczema	468	Bidder's organ of the toad, cyclic changes in	58
— metabolism	51	Biological abstracts, new journal	34
— production of mydriasis...	91	Blood calcium and adrenalin action	149
— the menopause	461	— as affected by insulin....	251
— blood reaction and vascular response to	351	— cells, sugar insulin.....	74
— clinical value of, in thyroid conditions	86	— chlorides in diabetes.....	363
— content of adrenals in thyroidless rats	470	— cholesterol in diabetes.....	367
— discharge and anaphylaxis...	45	— reaction and vascular response to adrenalin	351
— effect of, on amino acids and simple sugars	472	— sugar in diabetes in pregnancy	74
— — — phosphorous partition in muscle	468	— — thyroid disorders	497
— — — temperature of skeletal muscle	464	— — influence of adrenalin on...	467
— — — upon skeletal muscle...	464	— — tests in diabetes.....	366
— — — vagus center	354	Calcium metabolism and thyroid.	491
— increase and x-rays.....	355	Carbohydrate metabolism and medulliadrenalectomy	463
— influence of insulin upon secretion of	40	— — obesity	366
— — on arterial pressure and blood sugar	467	— — in thyroid disorders.....	497
— insulin and nitrogen metabolism	483	— utilization in diabetes.....	607
— liberation of, by electrically exciting medulla	41	Castrates, effects of prostate and testicular emulsions on.....	59
— pressor effect of.....	466	Castration and transplantation of testicles of fowl.....	358
— reflex secretion of.....	42, 43	— effect of early, on voluntary activity of male rats.....	141
— secretion, effect of stimulation of sensory nerves upon rate of	469	— — fractional, on the voluntary activity of male rats	145
— spectrophotometric study of..	242	— — on suprarenal cortex.....	49
— virtual	468	— in bats	244
Amyloidosis of the adrenals as a cause of Addison's disease....	45	— the fowl	593
Anterior pituitary and thyroid, development of, in pig foetus.	496	Cholesterine and thyroid, and their relation to phosphate change in blood adrenals and sexual glands	56
Anaphylactic shock, and parathyroid hypercalcemia	81	Corpus luteum	173
Anaphylaxis and adrenalin discharge	45	— — and Graafian follicles in menstrual functions....	604
Antithyreokrin, biological control of	84	— — — menopause	461
Arginine, and physiological activity of insulin.....	79	— — in hen and in mammals...	246
Arneth count, deflection of by thyroid injections	92	— — menstruation and pregnancy	195
Basal metabolism, and diseases of thyroid	495	— — structure of cells and changes during menstruation and pregnancy....	357
— — ovarian function	476	Creatine, creatinine and arginine in adrenaline action.....	241
— — voluntary activity	103	Cretinism, sporadic	376
— — in acromegaly	360	Cryptorchidism, experimental, effect on suprarenal cortex....	49
— — human diabetes	77	Dermatosis and glands of internal secretion	50
— — hypothyroid patient	611		

Diabetes and acromegaly.....	610	Diabetic metabolism and oral administration of sulphur.....	484
— hemochromatosis	377	— state, explanation of.....	35
— insulin	73	— preparation and management of surgical	73
— thyroid	497	— technique in management of.	35
— cholesterin in, and influence of insulin	78	Diet, influence on nucleoplasma ratio in adrenals of rat.....	598
— diagnosis and treatment.....	366	Dystrophia adiposo-genitalis in three brothers	607
— effect of substance A on blood sugar in	609	Emmenagogue action of ovarian hormone	245
— food tolerance in.....	252	Endemic goiter	159
— human, basal metabolism in.	78	— changes in thymus and thyroid in	159
— in children	73	Endocrine diseases, Falta, Wilhelm (Book Review).....	462
— pregnancy, blood sugar in.	74	— factors in oxalic acid metabolism	260
— insulin and surgery.....	250	— — — vigor	97
— — — carbohydrate treatment in	155	— glands, and experimental cocaine poisoning	53
— latent	27	— — — insulin	368
— lipaemia retinalis and insulin.	364	— — of rats in parabiosis.....	473
— mellitus, acidosis, coma and infections in	72	— — possible relation of to otosclerosis	52
— — and blood cholesterol.....	367	— — therapeutic action of roentgen rays on.....	355
— — — growth in children.....	485	— origin of hypophyseal obesity.	68
— — — hypoglycaemia	259	Endocrinopathies, ovarian heterografts in	64
— — — hypophysis	605	Ephedrin and epinephrin, quantitative comparison of.....	354
— — — myxoedema	89	— pharmacological effect of.....	241
— — — protein diet	367	Epinephrine and blood sugar...242	
— — — antiketogenic influence of insulin in	255	— — ephedrin, quantitative comparison	354
— — blood chlorides in.....	363	— hydrochloride, effect of, in lowering blood pressure...597	
— — dietetic treatment of.....	157	— influencing peripheral action..599	
— — etiology of	72	Eunuchoidismus, mulierum verus connatus, a case of.....	58
— — in three-year-old child....368		Eunuchs, nitrogen metabolism of.	359
— — insulin in surgical complications in	364	Exophthalmic goiter and myxedema	93
— — refractory to insulin.....	486	— — pathogenesis of	106
— metabolism of dihydroxyacetone in	251	Exophthalmos, Fröhlich syndrome and diabetes insipidus, case history of	54
— one thousand cases of.....	156	Female sex hormone.....	602
— refractory to insulin.....	608	Follicular fluid	246
— relation of tissue cells to....256		— — action of, on uterine contractility	602
— surgery in	71	— hormone, effect of light on...59	
— treatment of	35	— — — on old rat.....	479
— use of "synthalin" in.....	252	— — quantitative action of.....	357
— utilization of carbohydrate in.	607	Folliculine, oestrous and uterine contractility	476
— Vichy Spa treatment of.....	77		
Diabetes insipidus	247		
— — and kidney excretion.....	361		
— — — pituitary	70		
— — — treatment	480		
— — — tubercular lesion of posterior lobe of hypophysis	68		
— — — water intoxication.....	193		
— — exophthalmos and Fröhlich syndrome, case history of	54		
— — hereditary	364		
Diabetic, acidosis with negative ferric-chloride in urine.....	249		
— and mineral water.....	255		
— coma, treatment of.....	154		
— gangrene	76, 78		

Fröhlich syndrome, exophthalmos
and diabetes insipidus, case
history of 54

Gigantism, experimental, hypophy-
sis extract in 360

Glucose and insulin, effect of, on
respiration of spinal cord.... 368

— injection and tolerance..... 254

— tolerance in hyperthyroidism. 497

Glycemia and diseases of the
stomach..... 259

Glycosuria after insulin..... 253

Goiter, control of in Switzerland 95

— cretinism, experimental re-
searches on 90

— exophthalmic, and iodine.... 1

— heredity in 371

— pathologic anatomy of..... 95

— types and treatment of..... 431

— pathology of 582

— prevention 159

— of, incidence of in British
Columbia 89

— surgical treatment of (Book
Review) 34

— — — effect of iodine in... 86

Gonads and epilepsy..... 355

— implantation, effect on supra-
renal cortex 49

— in relation to hirsutism in
women 50

— of the toad, cyclic changes in 58

— seasonal size changes; thy-
roids and 161

Graafian follicles and corpus lu-
teum in menstrual function... 604

Headache and ovary..... 445

Heart movement, hormone of... 65

Hermaphroditism, three cases of
pseudo 61

Hemochromatosis and insulin
therapy 377

Hirsutism in women in relation
to gonads, suprarenals and hy-
pophysis 50

Hodgkins' disease 491

Hypertension, a manifestation of
insulin deficiency 260

Hyperthyroid reaction and ova-
rian insufficiency in Block's
syndrome 57

Hyperthyroidism and iodine.... 610

— effect of, upon plumage.... 374

— movements of crop of fowl in. 372

— studies in 374

— under iodine medication.... 160

Hyperthyroidized mammals and
thyroxine 376

Hypoglycemia, animal passage.. 364

Hypoglycemia, by adrenalin.... 48

— following insulin 366

— in children 365

— purification of insulin prepara-
tions 483

— without use of insulin..... 253

Hypophyseal colloid and cerebro-
spinal fluid 247

— diseases, anthropometric analy-
sis of growth disturbances
in 65

— obesity, endocrine origin of.. 68

— — of syphilitic origin..... 65

— operation, relief of acromegaly
by 65

Hypophysectomy and replacement
therapy 66

— in tadpoles, and iodofibrin,
iododestin and iodogladin
feeding 71

Hypophysis and anencephalic fe-
tus 606

— — diabetes mellitus 605

— — diuresis 70

— — epilepsy 355

— — fat metabolism 69

— — growth 70

— — internal secretion of ovary. 480

— — vigor 98

— comparative anatomy of.... 69

— effect upon intestine of extract
of posterior lobe of..... 248

— extirpation and blood pressure. 355

— extract, and dimensions of go-
nadectomized rats 362

— — biologic test of..... 481

— — effect of, on bone develop-
ment 362

— — in experimental gigantism. 360

— feeding in hypophysectomy.. 361

— growth and development.... 67

— in initiation of labor..... 481

— method of extirpation..... 457

— of hypogophis rostratus, de-
velopment of 68

— structure of pars intermedia
of 153

— tubercular lesion of, and dia-
betes insipidus 68

Hypopituitarism and optic nerve
atrophy 481

Hypothalamic center for adrenal
secretion 44

Hypothyroidism and gastric se-
cretion 261

— diagnosis and classification of 90

— management of patients with. 611

— relation of, to obstetrics and
gynecology 263

— urologic lesions with..... 438

— vertigo and deafness associ-
ated with 229

Inanition, effects of, on the testis	63	Insulin effect of, on blood calcium	251
Infantilism a pluriglandular insufficiency	51	— — — blood cholesterol, fat and sugar in nephrosis	78
Insulin action and diabetes	73	— — — mammalian heart	604
— — — thyroid	71	— — — respiratory quotient of dogs	252
— — — of	36	— — — weight of liver, spleen, kidneys, and lungs in fasting animals	79
— — — on disappearance of glucose and oxidations in blood in vitro	75	— glycosuria after	253
— — — pituitary extracts and adrenal mechanism	484	— hyperthyroidism	497
— activation of	155	— hypoglycemia in children	258
— administration of	35	— in man	366
— adrenalin and nitrogen metabolism	483	— in cardiac insufficiency in pregnancy	78
— and acetaldehyde formation	259	— crystalline form	363
— — — arterial blood pressure	74	— dermatology	364
— — — artificial hibernation in the woodchuck	155	— hepatic diseases	256
— — — blood sugar of corpuscles	74	— hypoglycemia in children	365
— — — carbon dioxide content	258	— surgical complications in diabetes mellitus	364
— — — diabetic lipaemia retinalis	364	— surgical diabetes	73
— — — diuresis	255	— influence of, on cholesterol in diabetes	78
— — — dysfunction of endocrine glands	368	— — — upon secretion of adrenalin	40
— — — fat formation	367	— like substances in malignant tumors	259
— — — glucose, effect of, on respiration of spinal cord	368	— oedema	368
— — — glycogen content of frog's muscle	258	— oral administration of	77
— — — hemochromatosis	377	— purification of, in hypoglycemia	483
— — — liver and muscle glycogen under various nutritional conditions	250	— physiological activity of, and arginine	79
— — — metabolism	51	— rapid disappearance from blood of	255
— — — naphthalinic cataract	258	— relation of tissue cells to	256
— — — pituitrin antagonism	610	— treatment	155
— — — refractory diabetes	608	— use of, in depancreatized dogs	609
— — — skin regeneration	482	Insulinemia, existence of a physiologic	257
— — — substance A	609	Internal secretions, disorders of, and neural progressive muscular atrophy	58
— — — thyroid	75	— — — glands of, and dermatosis	50
— — — thyroxin, antagonistic action of	483	Interstitial cells of embryonal ovary of horse	59
— — — vitamin in nutrition	608	Iodine and morbus Basedow	1
— — — antiketogenic influence of, in diabetes mellitus	255	— in different types of goiter	431
— — — arterial tension and glucemia	254	— — — surgery in primary hyperthyroidism	610
— — — by inunction	364	Islands of Langerhans in hyperthyroidism	497
— — — chemical composition of	363	— — — insulin and ligation of efferent vessels of pancreas	365
— — — content of pancreatic venous blood after hyperglucemia caused by glucose	260	— — — origin of	485
— — — — — and excitation of vagus nerve	256	— — — relation of, to surrounding structures	609
— — — diabetes and surgery	250		
— — — mellitus refractory to	486		
— — — effect of, in vagotonia	156		
— — — on amino acids and simple sugars	472		

Islands of Langerhans, secretion
and Golgi apparatus in cells of. 367
— studies on 610

Kidney permeability in hyperthy-
roidism 497

Lactation and pregnancy, effect
of, on blood calcium of thyro-
parathyroidectomized dogs. 233

— the glands of internal se-
cretion 480

— effect on blood calcium. 233

— injection of oestrin during. 152

Lecithin, action of adrenal tissue
upon 224

Liquor folliculi, uterine reaction
to 357

Liver and hemochromatosis. 377

— feeding in manganese toxemia. 363

— glycogen in hyperthyroidism. 497

— in pernicious anemia. 249

Melanoderma and lipoid meta-
morphosis 352

Menformon, female sex hormone. 602

Meniere's syndrome associated
with hypothyroidism 229

Menopause and carbohydrate me-
tabolism 497

— flushings of 461

Menstrual cycle, effects of ova-
rian therapy in 63

— function, Graafian follicles and
corpus luteum 604

— records and vaginal smears in
women 358

Menstruation, changes in cells of
corpus luteum during. 357

— corpus luteum and. 195

Metabolism, action of pituitary
extract on 246

— and pituitrin administration. 361

— effect of testis on, in chicken. 152

Mydriasis, production of, by thy-
ro-toxic blood serum and adre-
naline 91

Myrtillin, in hyperglycemia and
pancreatectomy 482

Myxedema and diabetes mellitus. 89

— exophthalmic goiter 94

— exophthalmic goiter, water
metabolism in 261

— myxedema therapy 494

Nitrogen metabolism, adrenalin
and insulin 483

— of eunuchs 359

Obesity and carbohydrate me-
tabolism 366

— hypophyseal, syphilitic origin
of 65

Obstetrics and gynecology, rela-
tion of hypothyroidism to. 263

Oestrin, injections of, during lac-
tation 152

— occurrence of in placenta. 603

Oestrous and x-ray sterilization. 479

— basal metabolism in rat dur-
ing 478

— cycle, correlation between me-
tabolism and 103

— in guinea pig. 359

— folliculine and uterine con-
tractility 476

— producing hormone, distribu-
tion in ovary of. 62

Organotherapy in retinitis pig-
mentosa 237

Otosclerosis and endocrine glands 52

Ovarian emulsions, influence of
upon nitrogen and gaseous me-
tabolism 60

— extract in abnormal growth. 473

— follicular extract, interruption
of pregnancy by injections
of 64

— substance, therapeutics of. 173

— grafts, histological modifica-
tion of 244

— heterografts in various endo-
crinopathies 64

— hormone 245

— and genitalia 246

— pro-oestrous develop-
ment 475

— attempt to purify. 478

— in blood 150

— injection, effect of, on me-
tabolism 104

— insufficiency and hyperthyroid
reaction in Block's syndrome 57

— preparations and menopause. 461

— therapy, effects of, in men-
strual cycle 63

Ovary ablation and fatigability of
muscle 476

— and headache 445

— intravital staining. 56

— placental feeding and ster-
ility 358

— vigor 100

— changes in, after x-rays. 475

— distribution in, of oestrous-
producing hormone. 62

— hormone and egg laying. 61

— influence of, on basal meta-
bolism 476

— internal secretion of. 152, 358, 603

Ovary, internal secretion of, and hypophysis	480	Parathyroid on anterior surface of thyroid.....	158
— of horse, embryonal structure of:.....	59	— pregnancy and lactation.....	233
— — mole, cyclic changes in....	602	— tetany and syphilis of.....	158
Pancreas ablation and myrtillin..	482	— — blood chemistry in.....	80
— and epilepsy.....	355	— — prevented by ammonium chloride	81
— — islands of Langerhans....	485	— — rôle of toxins in.....	489
— — thyroid, antagonism between	372, 487	— thyroid and growth.....	492
— — vagotonia	156	— — — ultra-violet light, action of on plasma.....	125
— — vigor	100	— transplantation and individual differentials	600
— carcinoma of islands of....	486	— removal and body temperature	53
— extirpation and thyroidectomy, and insulin action.....	71	Parathyroidectomy, effect of magnesium sulphate in.....	369
— function and ligature of ducts.	254	— in parent and skeleton changes in progeny	370
— diabetes and pregnancy.....	76	Pineal and vigor.....	98
— extract, effect of, upon cardiac contraction	74	Pinealectomy and anatomical changes in immature rats....	82
— hormone, influence of, on lymph	254	Pituitary and diabetes insipidus.	70
— islets and foetal thyroid....	84	— changes after section of right vagus	247
— suprarenal antagonism.....	76	— extract, action of, on metabolism	246
Parabiosis, endocrine glands of rats in.....	473	— — — — pregnant uterus of rabbit	66
Parathyroid ablation and calcium deficiency in experimental jaundice	487	— — — and cerebral circulation...	465
— — — healing of fractures....	369	— — — cholesterol metabolism.	248
— — — magnesium lactate....	490	— — — diabetes mellitus.....	480
— — — hydrogen ion concentration and carbon dioxide content of blood in.....	261	— — — feeding in children.....	606
— — — increase of methylguanidine in blood after.....	370	— — — influence of, on diuresis....	606
— — — lactation and growth.....	369	— gland and cholesterol metabolism	248
— — — activity, seasonal variations in.	161	— — autacoids of posterior lobe of	152
— — — and broken bones.....	25	— — homeotransplants and sexual maturity	154
— — — diseases of the bone.....	260	— studies on anterior lobe of.....	153, 247
— — — ultra-violet light.....	159	— transplants and genital system	64
— — — vigor	99	— — — and sexual maturity in the mouse	362
— deficiency, age, sex, weight and season, as factors in.....	117	Pituitrin and blood lipoids.....	360
— — — and calcium balance.....	493	— — blood sugar	248
— — — body growth and tooth calcification	493	— — carbohydrate metabolism	66, 361
— — — extract and calcium balance.	488	— — — and insulin antagonism.....	610
— — — excretion of phosphorus and calcium.....	80	— — — metabolism	51
— — — in relief of maternal tetany	81	— effect of, on amino acids and simple sugars	472
— — — use of, in hemorrhage....	157	— sensitivity of human organism	66
— — — gland in Anura, morphology of.....	81	Placental and ovarian feeding and sterility	358
— — — hormone, existence of.....	489	Pluriglandular insufficiency, the cause of infantilism.....	51
— — — preparation, properties and source of.....	488	Precocity of endocrine origin....	151
— hypercalcemia and anaphylactic shock....	81		
— injections and metabolism....	51		
— internal secretion of.....	79		
— medication in chronic nephrosis	494		

Pregnancy, action of pituitary extract in	66
— and lactation, effect of, on blood calcium of thyro-parathyroidectomized dogs.	283
— pancreatic diabetes	76
— thyroidectomy	374
— changes in cells of corpus luteum during	357
— corpus luteum and	195
— effect on blood calcium	233
— in rat, interruption of, by injection of follicular extract.	64
Prostate and testes emulsions, influence of on normal, castrated and thyroidectomized animals.	59
— — vigor	101
Pseudoepiphyses in endocrinology	601
Pseudohermaphroditism, catabolism of sex glands in a case of.	603
Retinitis pigmentosa and organotherapy	237
Roentgenotherapy in psychiatric and neurological diseases in childhood	56
Secretion, effects of injections of	40
Sex deficiency in hemochromatosis	377
— glands, and thyroid	373
— body temperature	53
— hormone from placenta	245
— organs and pituitary transplants	64
Sexual hormones, researches on.	57
Softening of striatum without choreo-athetotic symptoms.	474
Spaving, effect upon voluntary activity and metabolism	104
Spleen, size of, and thyroid secretion	95
Splenic constriction and muscular metabolites	466
— extracts, action of on blood corpuscles	82
Sterility in white mice	358
Suprarenal cortex, after castration, cryptorchidism and implantation of gonads	49
— (inter-renal) genital syndrome	151
— insufficiency	37
Syngenesiotransplantation in guinea pig	600
— the rat	601
"Synthalin"	252
— substitute for insulin	607
Syphilis, hereditary, thyroid alterations in	90

Testes and adrenals, influence of glycerine emulsions of, on tuberculous and senile patients.	53
— — prostate emulsions, influence of on normal, castrated and thyroidectomized rabbits	59
— — vigor	101
— effect of, on metabolism in chicken	152
— effect of vasa efferentia ligation on	62
— grafts in young goats	475
— — reaction of, in different environments	477
— histological changes in	245
— hormone, qualitative indicator for	603
— lipoids	56
— of inanition, overfeeding and thyroid gland on	63
Testicle transplantation and castration of fowl	358
Testicular emulsions, influence of, upon nitrogen and gaseous metabolism	60
— hormone production and cryptorchid testes	62
Tetany, latent postoperative.	373
— maternal, relieved by parathyroid extract	81
— thyroid feeding, atmospheric changes and	85
Tethelin, influence of, upon growth and longevity of white mouse	70
Thymic death during tonsillectomy	83
— hypertrophy, unusual case of.	491
Thymus and thyroid, and endemic goiter	159
— age of involution of, asserted non-existence of	18
— clinical manifestations of	82
— death	423
— function of	83
— growth of, in connection with the thorax, heart and lungs in swine	610
— thymicolymphaticus and thymic symptoms	490
— tumor in infant	491
Thyroid ablation and cardiac output	370
— — pregnancy	374
— — latent tetany after	373
— administration, bile pigment production and erythrocyte destruction	374
— — in senility	136

Thyroid adrenal apparatus, fever and infections.....	371	Thyroid gland feeding, effects of on the testis.....	63
— and anterior pituitary, development of, in pig foetus...	496	— — tuberculosis of.....	88
— — cholesterine in relation to phosphate change in blood, adrenals and sexual glands	56	— goitrous, effect of iodine on..	86
— — diabetes	497	— histological and microchemical studies on lipin content of.	89
— — epilepsy	355	— hormone and phagocytosis...	87
— — gonads, reciprocal size change of.....	161	— in treatment of goitre.....	431
— — insulin	75	— injections and metabolism....	51
— — — reaction	71	— — — the Arneth count.....	92
— — — influence of, on oxydases in different organs...	243	— innervation and secretory path of.....	262
— — lactation	480	— iodine compounds of.....	88
— — metabolisms	495	— medication in chronic nephrosis.....	494
— — pancreas, antagonism between	372, 487	— microscopic tubules in.....	372
— — reaction to adrenalin....	351	— occurrence of parathyroids on anterior surface of.....	158
— — thymus, and endemic goiter.	159	— parathyroid and growth.....	492
— — — antagonism of.....	491	— — and ultra-violet light, action of, on plasma.....	125
— — vigor	98	— pregnancy and lactation....	233
— — vitamin B.....	96	— preparations, evaluation of...	85
— antagonist, antithyreokrin....	84	— produces diabetes.....	89
— alterations in hereditary syphilis	90	— races, large and small, established by breeding.....	161
— conditions, use of adrenalin in	86	— relation of, to calcium metabolism	491
— deficiency, age, sex, weight and season, as factors in..	117	— removal and body temperature	53
— disease and cretinism.....	376	— secretion and size of the spleen	95
— disorders, carbohydrate metabolism in	497	— size, seasonal variations in..	161
— disturbances, diagnosis of, by interferometric blood test..	87	— transplantation and individual differentials	600
— dysfunction, value, of Kottman reaction in	262	— tuberculosis of.....	371
— effect of large doses of iodine on.....	263	Thyroectomized animals, effects of prostate and testicular emulsions on.....	59
— electrocardiogram, and pilocarpine	87	Thyroidectomy, adrenalin content of adrenals after.....	470
— extract and metamorphosis...	374	— and changes in growth of skeletal muscle	94
— — — potassium iodide, effect of on thyroid.....	261	— — skeletal muscle development	264
— — in abnormal growth.....	473	— — the Arneth count.....	92
— — — general endocrine insufficiency	472	— — tissue respiration.....	87
— experiments to increase hormone output of.....	493	— ante-mortem protein decomposition after.....	263
— failure, physiological failure of	89	— effect on basal metabolism...	103
— feeding and atmospheric changes in production of tetany	85	— indications for; results of...	376
— — — cardiac output	370	— its relation to cure of thyrotoxicosis	93
— — body temperature	53	Thyroparathyroidectomy and cod liver oil	262
— foetal, and pancreatic islets..	84	— effect of pregnancy and lactation on blood calcium of...	233
— gland and sex glands.....	373	Thyro-toxic blood serum and production of myriasis.....	91
— — cellular activity and structure in	371	Thyrotoxicosis and thyroidectomy	93

